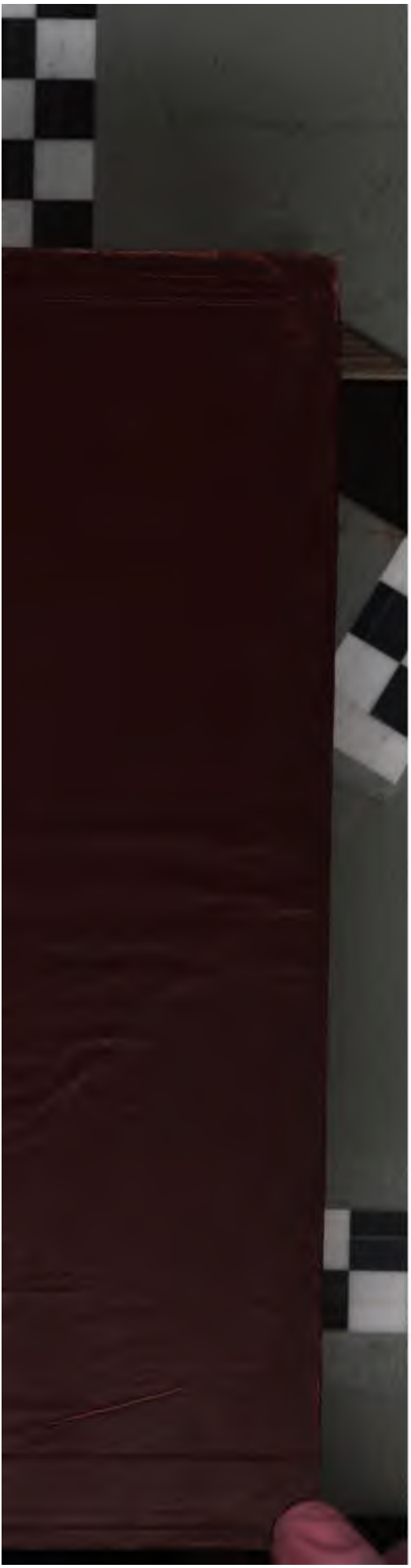

DIABETES MELLITUS

DESIGNED FOR THE USE OF PRACTITIONERS OF MEDICINE

BY

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I

NORMAL METABOLISM

THE functions of the living cells represent chemical changes within them and are dependent upon an interchange of nutrient and refuse material with the surrounding fluids. The sum of these various complex processes involved is termed metabolism. The cellular functions entail the expenditure of energy and also the wearing out of cellular substances, and the materials for the replacement of these substances and for the total energy needs must be furnished by food. The food requirements of the body, then, must cover the demands for energy expended as mechanical work, chemical work and heat, and also for the replacement of worn-out tissues.

Since the tissues are primarily composed of protein, it is evident that for their repair protein food becomes the chief essential; while either fats, carbohydrates, or protein can be utilized to furnish energy, only the protein can replace body tissue. Fat and carbohydrate contain the elements carbon, hydrogen, and oxygen; protein has these elements and also nitro-

gen, consequently nitrogen is commonly employed as the measure of the protein economy of the body, and the sum of the total metabolism can be estimated in terms of carbon and nitrogen. Because of the essential nature of the protein economy to the body it deserves more than passing notice. When protein undergoes digestion in the alimentary canal the resultant cleavage products are amino-acids, of which leucine and tyrosine are examples. The amino-acids are absorbed by the blood and conveyed to the various cells, where a resynthesis into protein takes place. This explains how the body is enabled to build up a number of different cellular proteins, each peculiar to some organ, out of the aggregate of amino-acids from protein food. The process is comparable to the various architectural designs that might be constructed from a set of toy blocks, hence the German term *Bausteine* (building stones) to designate these products of protein hydrolysis. The chemical differences between the proteins of various organs rest in the amino-acids that constitute them. Having this conception of protein anabolism in mind, it becomes at once evident that the food must contain the basis for a considerable variety of these acids, since the various tissues have different requirements. When the need of a vital organ is not met in the food supply, some less important tissue is sacrificed by nature to furnish

the material demanded; for example, during starvation the heart protein is preserved at the expense of the skeletal muscles. Nitrogenous food not only replaces body tissue but it may also serve as a source for a large part of the energy requirements. Carnivorous animals are able to do work and maintain nutrition on a diet composed essentially of protein. That man is unable to do so appears primarily due to his inability to masticate and digest the amounts necessary. When protein food is ingested in large amounts beyond immediate needs there is no general tendency on the part of the body to store protein as is the case with fat. Only the carbon is stored, as the nitrogen is recoverable in the urine. Experiments which will be detailed subsequently indicate that the carbon is saved to the body as glycogen. This failure of the tissues to store protein, except during definite periods of growth or convalescence, marks the chief peculiarity of nitrogen metabolism in the animal body. There is here a marked tendency to maintain an equilibrium between ingest and egest unless the amount of nitrogenous food is actually below the needs for tissue repair. On the other hand, when the intake is excessive the urinary nitrogen rises to a higher level until a balance is struck. Now the explanation for this is evident in the chemical structure of protein, which may be expressed as a chain of amino-acids the links of which

are broken in digestion. Amino-acids that are not utilized for the synthesis of new proteins are deamidized, that is, lose the NH_2 radicle and are thus transformed into fatty acids. The resultant ammonia from the amino-radicle becomes united with carbon dioxide and goes over into urea. Some of the fatty acids are transformed into sugar and stored as glycogen or fat if not required as fuel, while others are probably built up into fatty compounds without the intervening sugar transformation. In this manner the carbon of the surplus protein is reserved to the body.

There are many experiments recorded, both on man and on animals, which illustrate this tendency of nitrogen metabolism to establish an equilibrium between ingest and egest. When the caloric need of the body is made good by the use of carbohydrates and fat, the intake of protein food may be very small indeed (6 to 7 grammes N, equivalent to 37 to 44 grammes protein), and there then occurs a gradual fall in the body's nitrogen output until a balance is struck. Just how low the protein metabolism can be maintained over long periods without prejudice to health is not clear. Some believe as little as 0.1 gramme of nitrogen per kilo of body weight (50 grammes protein per day) is adequate for adults, but this standard is not generally accepted since it is less than half the amount computed to be necessary by

Voit. Studies of the nitrogen metabolism made upon man and animals during fasting have been very instructive in giving insight into the protein chemistry of the body. During the first few days of the fasting period there is a slow fall in the daily nitrogen excretion below the amounts excreted prior to fasting. During this period the body is burning its glycogen stores, and when these are consumed there is a temporary rise in the nitrogen output which indicates that body tissue is being expended. There is then a gradual fall to a low level which persists until death approaches. Between the twentieth and thirtieth days of his fast Succi excreted from 6 to 3.0 grammes of nitrogen per day, a loss to the body of 37 to 19 grammes of protein. As there was at this time no glycogen the necessary energy must have been made good by body fat. When there is a scant reserve of fat in the body the protein catabolism is higher—that is to say, more energy must be furnished by protein, and in this sense fat is a protein sparer. But fat will not be consumed in large amounts except under those forced conditions of metabolism exemplified in the fasting state. Carbohydrate is much more effective in saving body protein from consumption than is fat. Voit was able to demonstrate that while ingested starch lowered the nitrogen excretion considerably, fat did so only to a limited extent even

when the caloric value of the fat was greater than that of the starch. It appears, then, that there is a selective action on the part of the cells, and carbohydrate is burned by preference so long as available for the necessary heat production; in the absence of available carbohydrate fat will be utilized in order to conserve the more essential protein.

From this discussion it is apparent, first, that protein is qualitatively the indispensable food material of the body, and in its absence actual tissue destruction occurs even though the energy needs are met in other foods; second, that beyond the minimal requirement of protein the organism is able to utilize either fat or carbohydrate, and at least qualitatively it is indifferent which of these is available; and, finally, these foods are capable of acting as protectors to body tissue, saving it from destruction for heat demands.

The chief energy requirement of the body is for the maintenance of body heat. Rubner has shown that almost the entire potential energy of food leaves the resting body as heat. Kinetic energy and heat are developed through the oxidation of the various nutriment materials ingested, and this oxidation process in the animal body appears to be very definite and orderly and is probably specific for each of the three food materials. Tissue oxidations are seldom if ever direct in the sense conceived by Lavoisier, but

are effected through the agency of enzymes. In the case of carbohydrate and fat the end products of combustion are carbon dioxide and water, while with protein the urinary ingredients such as urea are still capable of yielding heat if oxidized;[1] that is to say, protein is not completely oxidized, its potential energy never completely developed, in contrast to fat which is burned to its ultimate end products.

As the total energy of the body is effected through the absorption of oxygen and the production of carbon dioxide it is possible, by measuring the oxygen used or the carbon dioxide produced, to compute the amount of heat developed during a given period. Commonly this energy is measured in large calories—the heat required to raise one kilogramme of water 1°C. The amount of heat produced by the healthy resting body varies with a number of considerations, chief among which is the size (surface area), radiation being relatively greater from small bodies. At rest this amount is about 32 calories per kilogramme body weight per day; under various degrees of activity of course it is proportionately greater. There is also a wide variation in diseased states; with fever metabolism is much increased and roughly proportionate to the rise in temperature, while, on the other

[1] According to Rubner 22 to 28 per cent. of the potential energy of protein is lost to the body through this incomplete combustion.

hand, in some disorders such as myxœdema the energy requirement is below the normal.

With respect to any morbid condition, then, we are concerned with metabolism from two points of view: first, quantitatively, since only by recognizing differences in the sum of energy demands can we arrange suitable dietaries to furnish the energy; and second, qualitatively. When through the failure of the organism to utilize some nutrient material in the normal way there arises increased demands for other forms of nourishment, or the by-products of the perverted metabolism are in themselves injurious; then we have conditions which not only influence the sum of the total energy demands but also induce many remote effects that become manifested in a clinical picture. In diabetes mellitus we find both qualitative and quantitative changes in metabolism, and an understanding of these is requisite to a comprehension of the disease and its treatment.

II

SOURCES OF GLUCOSE IN THE ANIMAL BODY

THE fuel of the animal body is chiefly carbohydrate. Under normal conditions demand is made first upon the carbohydrate stores to supply heat and energy for work, and so long as these stores are adequate there is slight call upon protein or fat. The latter may be regarded, so far as metabolism is concerned, as an emergency reserve. It is perfectly possible to maintain life at least on an adequate food supply of starches, with just sufficient nitrogenous food to replace the wear and tear of tissue breakdown—a little over 0.1 gramme of nitrogen per kilo body weight per day. It concerns us at present to ask whence this supply of carbohydrate is derived under various conditions of nutrition.

The carbohydrates in foods consist of starches (and the products of starch cleavage, *i.e.*, dextrins) and the simpler sugars such as saccharose, fructose, and glucose. In the course of their transit through the intestinal canal the more complex carbohydrates are broken down through the agency of the several amylolytic enzymes into simple hexoses (six carbon

sugars). The greater part of the sugars enter the blood stream as dextrose and levulose. It remains debatable whether any carbohydrate is absorbed in a more complex form than glucose; if any, it must be but in traces since the introduction into the blood stream of saccharose is followed by its excretion in the urine.[1]

During the period of digestion following a meal rich in carbohydrate the portal blood leaving the intestine contains much more glucose than the blood as it leaves the liver in the hepatic vein. The liver acts as a screen, removing the excess of glucose and storing it as glycogen, thereby protecting the general circulation and preventing loss through the kidneys. Other tissues, notably the muscles, are also capable of transforming glucose into glycogen and conserving it for future needs. When the supply of food is in excess of the immediate requirements of the organism the glycogen content of the tissues may become very large, but, as will be seen, glycogen is not the sole means of disposal of superfluous glucose since the transformation of carbohydrate into fat is one of the best demonstrated facts in physiology. That glycogen may be formed in the body from ingested carbohydrate was shown by the following experiment. Rabbits were kept without food for such a period as experience had shown to deplete the liver glycogen to

[1] Voit: Deutsch. Arch. f. klin. Med., 1897, 58, p. 523.

an insignificant amount; then after feeding substances rich in carbohydrate the animals were killed and the organs examined for glycogen. It was found that in rabbits so fed the livers contained much more glycogen than the livers in control animals.[2] It was also shown that the subcutaneous administration of glucose caused an increase in liver-glycogen,[3] and finally Grübe[4] noted that the perfusion of the liver with blood rich in glucose caused an augmentation of glycogen in the liver. We know too, that the muscles are capable of forming glycogen from glucose[5] and that the total muscle tissues can contain about the same amount as the liver.

At the present time no one questions the validity of the idea that glycogen can be formed from carbohydrates. The biological principle in this process is worthy of note since it is typical of many transformations in the animal body. Glycogen is a substance much resembling starch. It has the elemental composition and the same formula $(C_6H_{10}O_5)_x$ and is often called animal starch; it differs from starch, however, in many reactions. For the manufacture of this substance from starch the animal organism

[2] Pavy: Philosophical Transact., 1860, p. 579. Pflüger: Das Glycogen. Cremer: Ergeb. Physiol., 1902, p. 803.

[3] Voit: Zeit. Biol., 1891, 28, pp. 245 and 288.

[4] Pflüger's Arch., 1905, 107, p. 490.

[5] Külz; Pflüg. Arch., 1881, 24, p. 64.

proceeds to break down the latter polysaccharide into its simplest units, the hexoses, and from these by a form of synthesis glycogen is built up. Disregarding the intermediary steps the reactions are these:

$$\underset{\text{Starch}}{(C_6H_{10}O_5)_x} + H_2O = x\,\underset{\text{Glucose}}{(C_6H_{12}O_6)}$$

$$x(C_6H_{12}O_6) - H_2O = \underset{\text{Glycogen}}{(C_6H_{10}O_5)_x}$$

This is an example of one of the most characteristic biological reactions, hydration and dehydration, and it will often be met with in other relations.

The question arises at this point: Is the glycogen derived from glucose the same as that from levulose, or are they different? It is difficult to understand, from a chemical point of view, how dextrose and fructose can produce an identical glycogen, since the former hexose is an aldose containing the CHO group while the latter is a ketose marked by the CO group. Further, the transformation of one sugar into the other is a difficult procedure in the laboratory. Of course it is possible that these sugars may be transformed by quite different processes and no common compound be formed until glycogen is produced. It is often cited that in pancreatic diabetes levulose given in the food can form glycogen in the liver, while dextrose cannot, but more trustworthy experiments indicate that this is incorrect.[6]

[6] Barrenscheen: Biochem. Zeitschr., 1913, 58, 277.

Inasmuch as glycogen is not peculiar to the tissues of the herbivera it follows that there must be other sources for it than carbohydrate. At one time this subject was a matter for no little discussion among physiologists, and though it cannot be claimed at present that every step is demonstrated, still the principles involved are generally accepted. The fact is beyond dispute that animals fed exclusively on protein and fat store up large amounts of glycogen. At one time this glycogen was supposed to arise exclusively from the carbohydrate radicle in protein, but it was soon shown that this radicle could not possibly account for the amounts of glycogen found in the tissues of experimental animals.

There are two methods of approach to the problem: first, the direct method. In this method an animal is rendered glycogen free by one of several means—starvation, work, or strychnine poisoning. Then, after a suitable period during which but one sort of food, *i.e.*, protein, is fed, the animal is killed and the glycogen in the organs quantitatively estimated. If the glycogen found exceeds that of control animals, killed after starvation, this excess must have come from the food taken. The second or indirect method depends on the principle that foods which form sugar are indirect glycogen formers. In this method animals are made diabetic either with phlor-

hizin or by removal of the pancreas, and account is taken of the food eaten and the sugar produced (excreted).

The direct method was used by Bernard. He stated that glycogen was stored in the liver when only flesh was taken, and from this observation he argued that protein can be transformed in the animal body into glycogen. Bernard did not make proper allowance for the glycogen in flesh eaten, which may be as much as one per cent.

The most complete researches on the derivation of glycogen from protein as tested by the direct method are those of Külz.[1] This investigator in his work used pigeons and hens. It was observed that after two to four days' starvation the average amount of glycogen in the liver and muscles was 0.946 gramme per kilo body weight, and that after four to eight days' starvation the liver became glycogen free while the muscle glycogen averaged 0.716 gramme per kilo body weight, with 1.414 as a maximum. Külz used thirty-three birds in establishing his averages. The birds were fed from fifteen to twenty-five days on flesh powder which had been extracted until glycogen free. With the pigeons the glycogen content of liver and muscles was found to average 2.03 grammes per kilo. Subtracting from this the starvation maximum

[1] Reported by Pflüger: Arch. f. d. ges. Physiol., 1903, Bd. 96, p. 1.

(2.03 − 1.414), the positive increase amounts to only 0.616 gramme. This is a small amount, and it is possible to account for it in traces of glycogen in the meat too small to give reactions in tests for it, since an equivalent of 5 kilos of fresh flesh was fed. Then, too, a slight decomposition in the meat during the process of extraction would convert the glycogen into dextrin, which would escape detection (Brucke-Külz method). From these researches Pflüger concluded that " even with excessive flesh feeding no deposition of glycogen had occurred."

If it be shown that glucose may take origin in the animal body from protein the glycogen stores are explained. The solution of this question rests largely on experimental diabetes. It is owing to the classical researches of Von Mering and Minkowski that the experimental difficulties surrounding this question were overcome. When dogs are rendered diabetic by removal of the pancreas and are then given exclusively protein food the amounts of sugar excreted in the urine are much too large to be accounted for by any possible glycogen reserves in the body. The urinary sugar can have but two possible sources, the proteins of the food (and tissues) and fat. An experiment of Lüthje seems to demonstrate this point.[8] A dog weighing 5.8 kilos during twenty-five days after re-

[8] Arch. f. d. ges. Physiol., 1904, cvi, p. 160.

moval of the pancreas excreted 1176 grammes of dextrose on a carbohydrate-free diet. According to the average determined by Pflüger the maximum amount of glycogen the dog's body might have contained would be 232 grammes (5.8 × 40) but this would account for only 257 grammes of sugar, leaving 919 grammes (1176 – 257) unaccounted for. Von Mering noted that when his dogs were fed on meat and fat only, after the first three or four days the total daily excretion of sugar and nitrogen bore a constant relation to each other, which suggested a common origin for the sugar and nitrogen. This relation varies slightly, but in completely depancreatized dogs the ratio of sugar to nitrogen (D : N) is from 2.9 : 1 to 3.05 : 1.

The large sugar excretion which is observed for the first two or three days after the removal of the pancreas is derived from the glycogen stores in the liver and muscles, but if the animals be killed five or six days after the operation only mere traces of glycogen are detectable in these tissues, and this is so no matter whether food has been given liberally or withheld.[9]

It is evident, then, that after the first few days there are but two possible sources for the sugar excreted by

[9] Macleod: Recent Advances in Physiology and Biochemistry, 1906, p. 349.

depancreatized animals, namely, protein and fat. It is the opinion of Minkowski that the sugar is derived exclusively from protein. If the carbon in protein were converted into sugar, 100 grammes of protein would yield 113 grammes of grape sugar and 16 grammes of nitrogen. This would mean a ratio of seven (D : N = 7 : 1). But Minkowski's ratio is three. Two hypotheses suggest themselves in explanation: first, all the carbon in protein is converted into sugar but in depancreatized dogs a constant part of this sugar is destroyed in the body; second, only a part of the carbon in protein is converted into sugar. Minkowski and others have attempted to determine whether animals rendered diabetic by complete removal of the pancreas are able to utilize any dextrose. It was Minkowski's decision that ingested dextrose is entirely recoverable in the urine. Only moderate amounts can be given in this way, however, since large doses cause diarrhœa preventing absorption, and when the small dosage is used it is difficult to determine an increase of sugar in the urine because of the normal fluctuation of the sugar excretion in depancreatized dogs. Other investigators, however, have not accepted Minkowski's results, but have concluded that the organism still retains, after pancreatectomy, a slight ability to destroy dextrose; that is, all the administered dextrose does not appear in the urine, although the

greater part of it does.[10] It is believed by most physiologists that the sugar destroyed, if any, is of a negligible amount. The reasons for this belief are based upon the respiratory quotient found with depancreatized dogs. This quotient is so low that only protein and fat combustion would account for it. If no sugar or at most but traces of sugar are burned, then the first hypothesis falls and we are forced to conclude that only a part of the carbon in protein is converted into glucose. The possibility suggested by Minkowski that 45 grammes of sugar is the maximum derivable from 100 grammes of protein (100 grammes $\div$ 6.25 = 16 grammes nitrogen. $16 \times 2.8 = 44.8$), in accordance with the D:N ratio of experimental diabetes, rests chiefly on the respiratory quotient. The salient fact is that there is a constant relation between the nitrogen and sugar output, and this fact is the major support of the doctrine of the origin of sugar from protein. Until late in his life, Pflüger, the most exacting critic in this field of investigation, denied the origin of sugar from protein. He believed that the excess of excreted dextrose is derived from fat and advanced a complex explanation which is now only of an historical interest. On the basis of his own experiments by the direct method of

[10] Langstein: Ergebnisse der Physiologie, 1902, Bioch. Abth., p. 96; 1904, 1st Abth., p. 453.

glycogen accumulation Pflüger convinced himself of the formation of sugar from protein. The consensus of opinion at present accepts this transformation as demonstrated.

The work of Emil Fischer has disclosed that proteins are aggregations of various amino-acids linked together, and we know that in process of digestion the protein molecule is split up by trypsin into its simplest components, amino-acids such as leucine, tyrosine, alanine, etc. The question arises: Which, if any, of these acids are sugar formers? Kossel first called attention to the fact that some of these amino-acids—leucine, arginine, lysin—contain the same number of carbon atoms as dextrose. Kossel's idea,[11] later expressed by F. Müller, was that protein which yielded so much amino-acid could hardly contain a sugar radicle equal to 60 per cent., the inference being that sugar must be derived from some of these acids. The matter was first submitted to experiment by Knopf,[12] who gave an amino-acid, asparagine, to a dog partly poisoned with phlorhizin, and observed an appreciable increase in the amount of sugar excreted. In the meantime Lusk[13] demonstrated that, by suitable use of phlorhizin, dogs could be made to give a

[11] Kossel: Deutsch. med. Wochschr., 1898, xxiv, p. 581.
[12] Knopf: Arch. f. exper. Path. u. Pharmakol., 1903, xlix, p. 123.
[13] Lusk: Zeitschr. f. Biol., 1898, xxxvi, p. 82.

D : N ratio of 3.65 : 1. This ratio, higher than Minkowski's, would indicate even less utilization of glucose in the dog poisoned with phlorhizin than is the case in the dog whose pancreas is removed. Since the operation of complete removal of the pancreas is a difficult one, this discovery of Lusk was important, and the method he devised has yielded very interesting results. For a number of amino-acids the data at hand point to the conclusion that they are dextrose formers. This is the case with glycocoll, alanine, aspartic and glutamic acids, to mention some of the more important acids.[14] The investigations of Embden and Salomon,[15] Baer and Blum,[16] and Glaessner and Pick,[17] antedated some of Lusk's work but none of their investigations was conclusive since in all, the animals were but partly diabetic. Of no less interest is the observation that leucine [18] and tyrosine [19] do not undergo transformation into dextrose.

The metabolism of leucine and tyrosine and the

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[14] Lusk: Zeitschr. f. physiologische Chemie, 1910, 66, p. 115; Ergeb. f. Physiol., 1912, *loc. cit.*

[15] Embden and Salomon: Beitr. z. chem. Physiol. u. Path., 1904, v, 507; vi, p. 63.

[16] Baer and Blum: *idem*, 1907, x, pp. 80–104.

[17] Glaessner and Pick: *idem*, 1907, x, p. 473.

[18] Embden, Salomon and Schmidt: Beitr. z. chem. Physiol. u. Path., 1906, viii, pp. 121–156. Baer and Blum: Arch. f. exp. Pathol. u. Pharm., 1906, 55, pp. 89–111.

[19] Lusk: *vide supra.*

formation from them of β-oxybutric acid will be discussed in another section.

It would be of considerable interest to have knowledge of the intermediary substances through which an amino-acid must pass on its way to glucose. The data at command allow only inferences. Some clue to the possible course of events was given by the observation (Neuberg) that, after the ingestion of alanine, lactic acid appears in the urine of rabbits,[20] while glycogen is deposited in the liver. It has also been shown that in diabetic dogs *d*-lactic acid [21] is completely converted into dextrose. The chemical change required for the transformation of alanine to lactic acid is an easy step and one in accord with other known transformations—

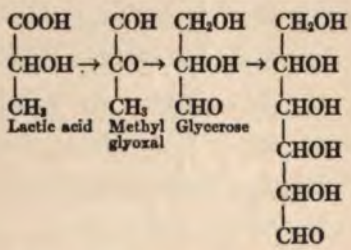
$$\begin{array}{l} CH_3 \\ | \\ CH\text{-}NH_2 + H_2O \\ | \\ CO\text{-}OH \\ \text{Alanine} \end{array} = \begin{array}{l} CH_3 \\ | \\ CHOH \\ | \\ COOH \\ \text{Lactic acid} \end{array}$$

The substitution of an hydroxyl (OH) group for an amino (NH_2) group (deamidization) is a process met with frequently in animal chemistry.

It is more difficult to explain the origin of sugar from lactic acid. All one may do at this time is to state the hypotheses that have been advanced in explanation, but for which substantial basis is still lack-

[20] Neuberg: Arch. f. Physiol. u. Pathol., 1908, p. 473.
[21] Mandel and Lusk: Am. Jour. Physiol., 1906, xvi, p. 129.

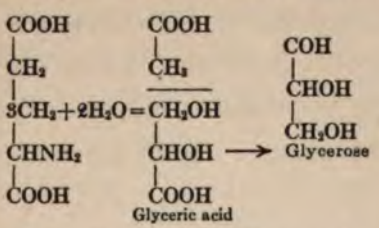
ing. One conception (Stoklasa [22]) is that the lactic acid is broken up into alcohol and CO_2. This can scarcely be the case since alcohol is not a sugar former in human or experimental diabetes. According to another hypothesis lactic acid is transformed into glyceric aldehyde with methylglyoxal as an intermediary product (Wohl [23]) while Löb [24] believes that



even simpler substances than lactic acid are the building stones of glucose, namely, that the lactic acid goes to form acetol and this last in turn to formaldehyde from which glucose is constructed. This idea would bring animal and plant physiology in accord since it is believed that formaldehyde is the basis for sugar production in plants (Baeyer's hypothesis). It is not probable that sugar formation from amino-acids takes place through lactic acid in all cases. At least such a transformation would seem indirect from a purely chemical standpoint. For example, glutamic

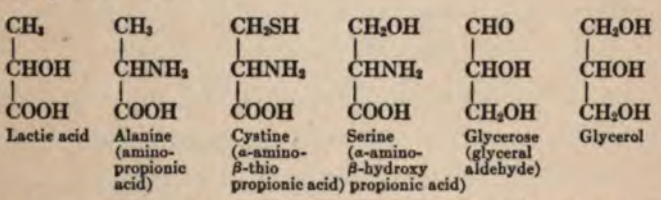
[22] Stoklasa: Beitr. z. chem. Physiol. u. Pathol., 1903, 3, p. 60.
[23] Biochem. Zeitschr., 1907, v, p. 45.
[24] Löb: Biochem. Zeitschr., 1908, xii, p. 78.

acid, following known laws, would break at the β-carbon atom, glyceric and acetic acids resulting—



and from the glyceric acid to glucose is an easy step.

Positive knowledge in this field of bio-chemistry is so deficient that no conclusion can be made and we must be content for the present in stating the general principles which seem to apply to various possible processes. A mere comparison of several substances recalling to mind the ease with which ammonia groups are added or abstracted is sufficient to indicate the many possibilities:



Formation of Sugar from Fat.—While the formation of fat from sugar is one of the best attested facts in physiology the reverse process as applying to animals has been the source of no little dispute. One of the earliest observations relating to the change of one food stuff into another was on the fat formation in ripening

seeds. We know that, while unripe seeds contain large amounts of carbohydrate and but mere traces of fat, the ripened seed contains much fat and but little carbohydrate. How definite this change is, is shown by the following analyses of nuts by du Sablon.[25] The figures are parts per 100.

	Oil	Glucose
July 6	3	7.6
August 1	16	2.4
September 1	59	0
October 4	62	0

We also know that during the germination of seeds the fat gradually disappears while carbohydrates take their place; that is, the process is reversed. There is no doubt, then, in so far as plants are concerned, of the transformation of fat into carbohydrate. With animals we are nearly convinced that ingested carbohydrate in excess of demand is in part stored as fat. The difficulty lies in the reversal of the process. At once it may be conceded that there is no more difficulty in its chemical aspect in understanding the transformation of fat into sugar than the origin of sugar from protein. Moreover, it is argued by the advocates of this theory that the process involved is one dependent on enzyme activity and enzymes are reversible in their action. In the first place it is difficult to conceive why this process is necessary since, so far as anything is known, the muscles might use fat directly as a source of

[25] Compt. rend., 1896, 123, p. 1084.

energy, and according to Zunzt the transformation of fat into sugar before combustion would entail a loss in energy of nearly 30 per cent. The methods employed in the investigation of this question are the same as those used for the determination of the origin of carbohydrate from protein: namely, the direct, depending on storage of glycogen, and the indirect, depending on the sugar excreted in diabetic animals.

It is now a matter of common observation that an increase of fat in the diet of a diabetic subject does not increase the amount of sugar excreted in the urine. The observation of Hübner illustrates this point in a diabetic patient. The albumen of the diet was decreased and at the same time the fat was increased. The sugar excretion fell with the diminished protein ingest.

176 gms. albumen + 150 gms. fat = urine-sugar, 51 gms.
176 gms. albumen + 319 gms. fat = urine-sugar, 50 gms.
98 gms. albumen + 315 gms. fat = urine-sugar, 7 gms.

The fact that the ingestion of large amounts of fat does not increase the urinary sugar is attested by numerous experiments and the daily practice of physicians who treat diabetic patients. But when we examine this evidence it proves nothing in so far as the question of the origin of carbohydrate from fat, and for this reason: food substances are utilized by the animal organism with varying degrees of facility. For heat and energy carbohydrates are burned first,

they are the fuel of preference, and so long as carbohydrate is available, be it circulating sugar or stored glycogen, there will be little demand on other food materials. When the carbohydrates are lacking—deprivation in food or depletion of glycogen stores—the proteins are next attacked as a source of energy. The fats remain chiefly a last reserve material. Thus it becomes evident that a surplus of fat in the diet does not of necessity enter into metabolism but is stored as fat in the tissues. However much fat be ingested, it will not be consumed for energy unless the other sources of heat are deficient. This is sufficient to explain why Hübner's results are not so vital as they at first seem. As Pflüger put it: " The extent of protein metabolism is dependent on the protein supply; while fat metabolism is independent of the fat supply." [26]

Voit was able to demonstrate that fat metabolism ceased as soon as a sufficient supply of protein be fed. This explanation suffices to show why the negative results of Hübner afford inadequate evidence against the possible origin of sugar from fat.

Fat is a compound of glycerol and fatty acids, and the relation that each of these substances bears to sugar formation must be separately examined. That glycerol can lead to sugar formation has been shown

[26] Pflüger: Das Glycogen u. s. w., p. 223.

even more conclusively than sugar formation from protein. This happens because glycerol can be fed to animals in extremely large doses. The very marked increase in sugar excretion which follows on the ingestion of glycerol has been proved for human (Külz) and experimental (Lüthje) diabetes.[27] But it is not believed that neutral fats necessarily undergo a saponification into fatty acids and glycerol prior to metabolism.

We may now ask: On what evidence does the hypothesis rest that fat may give origin to sugar in the animal body? We have noted that there is no *a priori* reason why this should not be the case. The theory owes its first impetus to the support of Pflüger, who never abandoned it. The adherents of the doctrine at present offer in its support the unaccountably high D : N ratios which have occasionally been observed in both experimental and human diabetes; ratios of glucose to nitrogen of eight, or of even twelve, are on record. If all the carbon in protein were convertible into carbohydrate, 100 grammes of protein would produce 135 grammes of sugar (100 grammes protein, 16 grammes nitrogen), which would be equivalent to a D : N ratio of eight. It is quite certain that so much sugar is not yielded by protein. But it is not demon-

[27] Of interest here are the experiments of Fischer in producing a simple sugar, triose, from glycerol.

strated what percentage is the maximum yield; there are differences of opinion which indicate always that the results of experiments are equivocal. Now it is quite evident that until it is known what is the amount of available sugar from protein—what is the highest D : N ratio—this ratio is a broken reed as a support to an hypothesis. On the other hand, in some of the observations, at least where high ratios have been found in human diabetes, sufficient deduction for ingested carbohydrate has not been made. The investigators have been deceived.

In experiments with animals where a ratio higher than 3.6 has been observed it has been always easy to find some possible error in the mode of conduction of the experiment. In both experimental pancreatic and phlorhizin diabetes a standard procedure has been worked out by Minkowski and by Lusk, and if the conditions these experimenters have adopted are not fulfilled almost any ratio is possible. In pancreatic diabetes the pancreas must be completely removed—it is not safe to leave a vestige of tissue if Minkowski's ratio of 2.8 is to be attained. With phlorhizin diabetes the drug must be given frequently and the animal must be rendered glycogen-free by exposure to cold. Lusk has found that all preparations of phlorhizin are not equally trustworthy. When these conditions are fulfilled the ratios have usually been secured. With

depancreatized dogs Minkowski found 2.8, while Lusk, in dogs completely freed of glycogen, by means of phlorhizin secured a ratio of 3.6. Magnus-Levy believes the latter figure represents the maximal sugar production corresponding to one gramme of nitrogen. The respiratory quotient found with completely phlorhizinized dogs indicates that no carbohydrate is being burned, which is strong evidence in favor of Lusk's ratio of 3.65.

The condition of affairs in human diabetes, in regard to the origin of the excreted carbohydrate, may be the same as in experimental animals and is usually assumed to be so. The metabolism in human diabetes may, however, be different, for anything known to the contrary, from that of the experimental disease. To throw any light upon the question of the origin of sugar from fat only the severest types of human diabetes are of use for study, since the others retain considerable ability to utilize carbohydrate. Even with the severe cases where death results from coma, the organs frequently contain some glycogen, and it would be quite impossible to assert that excess of urinary sugar over the theoretical amount arising from protein had not come from glycogen rather than fat unless a most rigid diet be adhered to for a considerable period. The author has had occasion to study several diabetic patients where the ratio of

sugar to nitrogen excretion appeared at first to be over 3.6, but in every instance a strict control of the diet by competent special nurses has resulted after a day or two in a fall of sugar excretion to a 3.6 ratio.[28] Until we know with the highest exactness what the maximal ratio may be—in other words until it is known what is the largest amount of sugar attributable to protein—it does not seem probable that we will be able to learn whether fat may yield a slight amount of sugar. The diabetic patient is for several reasons an extremely difficult subject for these experiments. It is usually impossible to restrict him for a period of a week to a fat-protein diet, hence we cannot be sure that he is not eliminating as glucose previously stored glycogen. This rules out those cases where carbohydrates have been fed in known amounts. Again, only under the conditions of a most carefully conducted experiment can the possibility of nitrogen retention be excluded.

The complexity of the question is evident from this cursory summary, and it is sufficient to say at present that the problem of the formation of sugar from fat has not been substantiated. Endeavors have been made to support the thesis of the origin of sugar in fat by respiration calorimetric experiments,

[28] Mendel and Lusk: Deut. Arch. f. klin. Med., 1904, 81, p. 472. Foster: Deut. Arch. f. klin. Med., 1913.

but with no convincing result.[29] A discussion of these experiments will be considered under the subject of respiratory quotients.

If fat can be transformed at all into sugar it must be only in the most insignificant amounts, and this statement is abundantly substantiated by a crucial experiment of Lusk.[30] If sugar can be derived from fat then those conditions which increase the catabolism of fat would increase the production of glucose. Using dogs completely under the influence of phlorhizin, Lusk induced an increase of 60 per cent. in the fat catabolism by exposure to cold in one set of experiments, and in another series by mechanical work the fat catabolism was doubled without in either case increasing urinary glucose over that derived from protein.

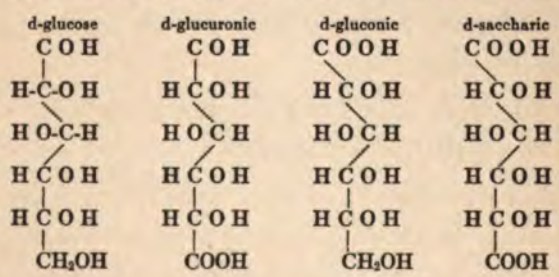
These experiments refute decisively the theory of Von Noorden that appreciable amounts of sugar result from fat catabolism.

A large part of the energy required by the body is derived from carbohydrates and some consideration of the possible ways in which this energy is developed remains to be mentioned. All carbohydrates are converted into simple sugars before combustion in the tissues. The possible modes of oxidation of glu-

[29] Grafe u. Wolf: Deut. Arch. f. klin. Med., 1912, cxvii, p. 201.
[30] Amer. Jour. Physiol., 1908, 22, p. 162.

cose must conform to the known facts that the end products are carbon dioxide and water, and that by the combustion about four calories are developed for each gramme of glucose burned. This oxidation probably takes place through a number of stages, and, because relatively too small amounts for detection of any substance resulting from the cleavage are present at any one moment, our knowledge of these stages is neither clear nor exact. Based upon the reactions which take place *in vitro* when glucose is subjected to oxidizing reagents, and upon the analogy with fermentation, various hypotheses have been advanced to account for the combustion in the tissues. According to these hypotheses this combustion may be classed as direct and indirect oxidation.

In direct oxidation glucose might involve oxalic acid, *d*-glucuronic, *d*-gluconic, or *d*-saccharic acid.



It is generally considered that oxalic acid cannot be a normal step in glucose oxidation in the body. Neither gluconic nor saccharic acids have been found in ani-

mal tissues and they do not behave in the body in a way that supports the hypothesis that the normal oxidation of glucose proceeds through these steps. The fact that they are burned in the diabetic organisms does not of necessity argue against this hypothesis, however, since it might lie in the initial step that the diabetic organism meets its difficulty. These statements do not apply to glucuronic acid, as this acid occurs in normal urine and there seems no question of its derivation from glucose. The amounts in the urine may be increased by the administration of drugs such as camphor and, notably, by thymotin-piperidid. Animals may be protected from lethal doses of the latter by giving large amounts of carbohydrate foods.[31] The question at issue is whether glucuronic acid is a normal intermediary product in sugar combustion combining in the organism with substances like camphor, or whether these drugs in some way pervert the normal course of catabolism to the formation of glucuronic acid. No definite answer can be given to this question at present.

Another conception of the mode of carbohydrate combustion in the body is based upon the analogy of alcoholic fermentation. In the transformations that occur in the process of alcoholic fermentation it is known that lactic acid is found as an intermediary

[31] Mayer: Zeit. f. physiol. Chem., 1900, 26, p. 256.

step, and probably methylglyoxal also. A basis for the hypothesis lies in the fact that from acetol lactic acid is derivable with methylglyoxal as the intermediary substance. Applying these considerations to the cleavage of glucose in the body, formulæ might be written as follows:

Glucose	X	Methyl-glyoxal	Lactic acid	
CHO	COOH	COH	COOH	CO_2
CHOH	CHOH	CO	CHOH	CH_2OH (alcohol)
CHOH	CH_2	CH_2	CH_3	CH_3
CHOH	CO	COH	COOH	CH_2OH
CHOH	CHOH	CO	CHOH	CH_3
CH_2OH	CH_2	CH_3	CH_3	CO_2

This scheme requires the interpolation of a formula between glucose and glyoxal which is purely hypothetical. For the rest the transformations occur with ease and in accord with known chemical processes. The evidence deduced by muscle analyses in support of this theory is none too strong,[32] however. Lactic acid is found in muscle, especially after exercise, and the amounts recoverable after autolysis of muscle are so large as to make the derivation from glucose most probable.[33] Ethyl alcohol has also been detected in muscle but only in traces.

At the present time we must confess that we are

[32] Asher and Jackson: Zeitsch. f. Biol., 1901, 41, p. 393.

[33] Magnus-Levy: Beitr. z. chem. Physiol. u. Pathol., 1902, 2, p. 261.

quite without sufficient data to form any clear conception of the breakdown of the glucose molecule, and it is probable in the initial step in the destruction of glucose that the essential deviation of the diabetic from the normal becomes manifest. Certainly the diabetic organism is usually able to handle the cleavage products of glucose. The inability to effect the first cleavage might rest in a change in the cell where oxidation is effected or in the absence of an activator. In the light of our knowledge of other vital processes we must assume the dependence of these changes upon zymases elaborated in one class of cells, perhaps the muscle, and in order to effect their function probably requiring an activator or hormone secreted perhaps by quite remote and different cells.

III

EXPERIMENTAL GLYCOSURIA

THE production of glycosuria in animals, while it has not completely solved the questions of the etiological factors in human diabetes, has, however, served a most important purpose in enabling physiologists to gain some insight into normal carbohydrate metabolism and the various influences that control this function. Chronologically, the " puncture diabetes " or *piqûre* discovered by Claude Bernard is the oldest method we have of inducing glycosuria. Bernard noted that if a needle be inserted into the medulla at the inferior part of the calamus scriptorius there ensues an excretion of sugar in the urine. This glycosuria persists for a variable length of time, commonly several hours. It was further observed by Bernard that glycosuria follows *piqûre* only when the animals are in a normal state of nutrition; and that it is entirely inhibited by fasting for a suitable period previous to the experiment. The meaning of this is explained by the fact that starvation frees the liver of its glycogen. There is no consequent glucose excretion unless the liver contain glycogen. Following puncture the blood sugar increases. *Piqûre* glyco-

suria is then an example of increased glycogenolytic function in the liver. Some of the nervous mechanisms which influence this form of melituria were remarkably well shown by Bernard's investigations.[1] It was noted, for example, that division of the vagi did not prevent the glycosuria due to *piqûre* and that stimulation of the peripheral stump of the vagus had no effect. Stimulation of the central stump, however, induces glycosuria. Bernard observed that the livers of experimental animals showed hyperæmia and he conjectured that the nervous influence operated in some way through the circulation. The researches of Eckhard [2] made it clearer that the medulla acts as a reflex centre in the production of this form of glycosuria. Stimulation of any afferent nerve fibre will cause transitory glycosuria. This has been shown best with the vagus. If the central stump be left accessible after the nerve is divided Eckhard demonstrated that electrical stimulation will cause a transitory glycosuria even several days after the nerve has been divided. It is requisite in this case as with *piqûre* glycosuria that the animals be well fed. Sugar may be caused to appear in the urine independent of punc-

[1] Cl. Bernard: Leçons sur le Diabète et la Glycogenese animale, pp. 375-380. Paris, 1877.

[2] Eckhard: Beitr. z. Anatomie u. Physiol., 1869, IV, p. 4.

ture of the medulla by cutting the lower cervical or upper thoracic sympathetic ganglia.[3]

It is next of importance to consider the efferent impulses from the medulla and whether these impulses concern the liver glycogen only. In this relation it has been commonly stated that either (1) cutting the splanchnic nerves at their entry into the abdomen, (2) section of the spinal cord above the first thoracic root, or (3) division of the upper three thoracic nerve roots, prevents the glycosuria [4] resulting from *piqûre*. These observations have been taken to mean that the path for the efferent impulses from the "diabetic centre" in the medulla is by the cord as far as the upper thoracic region, then by the spinal roots and rami-communicantes in the lower cervical or superior sympathetic ganglion. As glycosuria usually follows stimulation of the great splanchnic nerve but is prevented by division of all the nerve fibres leading to the liver, Pflüger believed the glycogenolysis to be a result of nerve stimulation. That the problem might not be so simple of solution was suggested in the work of Mayer,[5] who failed to secure *piqûre* glycosuria when

[3] Schiff: Untersuchung über die Zuckerbildung in der Leber u. den Einfluss des Nervensystems auf die Erzeugung des Diabetes. Würzburg, 1859.

[4] Eckhard: *loc. cit.* Laffont, cited by Pflüger: Arch. f. d. ges. Physiol., 1903, 96, p. 1.

[5] Mayer: Compt. rend. Soc. Biol., 1908, 60, p. 1123. Kahn: Pflüger's Arch., 1909, pp. 128, 519.

the adrenals had been removed from dogs and rabbits; and it has also been reported that stimulation of the splanchnic nerves fails to elicit glucose excretion if the adrenal glands are previously removed from the animal.[6] Many of these experiments have been repeated and elaborated by Macleod[7] and his pupils, with the conclusion that removal of the adrenals prevents the hyperglycogenolysis which ordinarily results from stimulation of the great splanchnic nerve. This fact does not indicate, however, that the secretion of the adrenals is the direct cause of the hyperglycæmia, since, with complete section of the hepatic plexus, splanchnic stimulation is not usually followed by hyperglycæmia. Still, the adrenals seem to be requisite for the production of hyperglycæmia and glycosuria as their removal effectually prevents the usual glucose excretion following on stimulation of the hepatic plexus. Some of the difficulties in interpreting the results of these experiments will be cleared away as we proceed. It has been attempted to explain *piqûre* and neurogenous glycosuria by supposing the enzymes governing glycogenolysis in the liver are under nervous control. An attempt to measure the ferment content of the liver before and after *piqûre* brought

[6] Gautrelet and Thomas: Compt. rend. Soc. Biol., 1909, 67, p. 233.
[7] Macleod and Pearce: Amer. Jour. Physiol., 1912, 29, p. 419.

forth no convincing differences [8] because the activity of an enzyme depends not alone on its quantity but also upon the conditions (acid, etc.) under which a constant amount of ferment is acting.[9]

In the experiments that have been already outlined the idea has usually prevailed that the stimulating impulse must proceed centrifugally in order to produce the result observed—glycogenolysis and glycosuria. As a rule no special caution has been exercised to the end of blocking centripetal stimuli. The failure to consider this possibility explains some of the discrepancies in results. If the spinal cord and both vago-sympathetic trunks are divided, all nerve connections to abdominal viscera are interrupted. Under these conditions stimulation of the cervical sympathetic ganglion induces glycosuria. Likewise the same form of [10] stimulation induces glucose excretion when the cord is cut and the animal poisoned with nicotine. If the posterior lobe of the hypophysis (pars nervosa) has been removed there is no melituria even though the nerves are intact; conversely direct electrical stimulation of the pituitary induces glycosuria. These observations make it appear probable that *piqûre* glycosuria is brought about by discharging into the

[8] Bang: Hofmeister's Beiträg., 1907, 9, p. 408; 10, p. 1.

[9] Macleod: Amer. Jour. Physiol., 1911, VII, p. 403.

[10] Weed, Cushing, and Jacobson: Bull. Johns Hopkins Hospital, 1913, XXIV, p. 40.

circulation some substance contained in the posterior lobe of the hypophysis. This discharge can be effected by nervous stimulation or mechanically. The meaning of these experiments is that the hypophysis (pars nervosa) is essential to *piqûre* glycosuria, and the mode of operation of the puncture is in some manner connected with a discharge of the internal secretion of that gland. Two glands of internal secretion then, the adrenals and the pituitary, are essential in *piqûre* glycosuria; the removal of either effectually prevents the glycogenolysis which ordinarily follows the Bernard puncture. What inter-relation these glands may have to each other we are at present only able to conjecture. Further experiments are required to elucidate this most interesting and complex problem.

The effect of adrenal extract in causing sugar to be excreted in the urine as noted by Blum [11] has been confirmed by many investigators, but Herter and Wakeman gave the first intimation of the significance of the phenomenon by showing that sugar appeared in the urine after painting the pancreas with adrenal extract, whereas similar applications to the other organs were not invariably followed by this effect. Before following this line of thought further some of the effects of adrenal extract on the sugar storehouse must be noted.

[11] Blum: Deuts. Archiv f. klin. Med., 1901, LXXI, p. 146.

The glucose excretion appears to depend upon the concentration of epinephrin in the blood, hence the effect of a single administration is not of long duration. The immediate cause of the glycosuria is that the blood sugar is increased in amount; this hyperglycæmia, in turn, being the result of the rapid transformation of stored glycogen into circulating sugar. Epinephrin glycosuria causes a rapid disappearance of hepatic glycogen, but according to some investigators muscle glycogen is exhausted even more rapidly.[12] This has been disputed, however. That epinephrin fails to produce glycosuria when the glycogen stores are depleted is evidenced by those experiments where the animal was first rendered glycogen-free by fasting and phlorhizin. This procedure would deprive the animal of its glycogen; and if now epinephrin be administered but little if any excess glucose appears in the urine.[13]

These experiments give the most probable interpretation of epinephrin glycosuria as an increased glycogenolysis. If this explanation be correct this form of experimental diabetes is quite similar to that of *piqûre* in so far as the source of the sugar is concerned. It is quite possible, however, that there may

[12] Kutschmer: Arch. f. exper. Patholog. u. Pharm., 1907, 57, p. 423. Agadshanianz: Biochem. Zeitschr., 1906, 2, p. 148.

[13] Ringer: Jour. Exp. Med., 1910, 12, 105.

be also a diminished destruction of glucose. In any case the deprivation of the body of a large part of the available glycogen as a result of epinephrin glycosuria would excite an increased protein metabolism as noted by Kraus and also by Eppinger. The chief points of relation between the *piqûre* diabetes and that induced by epinephrin are then: (1) both depend on the presence of glycogen in the tissues; (2) *piqûre* is inoperative after division of the splanchnic nerves, while epinephrin is active; (3) *piqûre* is inoperative after removal of the adrenal glands. The latter fact in particular, as will be seen in connection with pancreatic diabetes, leads to an attractive theory which would explain *piqûre* glycosuria as dependent upon adrenal secretion for its result. There are also some experiments to be mentioned which are most interesting, but the results cannot at present be accepted as facts because sufficient confirmation is yet lacking. On some of these inadequate foundations theories of human diabetes have been based. Some of the observations already mentioned give an intimation that the glycosuria resulting from adrenal extract and that from injuries to the nervous system are in some way closely related. This idea would be in accord with current theories of the chromaffin system. Epinephrin according to several investigators produces its effects

through the peripheral sympathetic nerves.[14] The sole difference, then, in the two types of glycosuria would be that in the one case, *piqûre,* the excitation is central; while in the other, epinephrin, the excitation is peripheral. This conception of epinephrin action is, however, disputed.[15] If the action of epinephrin be primarily through the sympathetic system then any substance which temporarily paralyzes this system would in consequence prevent adrenal glycosuria. Nicotine is believed to depress the sympathetic system and Hirayama [16] reported experiments where the glycosuria due to epinephrin was prevented by nicotine. Likewise Eppinger, Falta, and Rudinger [17] found that pilocarpine prevents the glycosuria due to epinephrin. This latter observation involves a second hypothesis which will be best considered in relation with pancreatic diabetes. It is quite conceivable that the effects of nicotine and pilocarpine, both of which are vaso-dilators, are explicable in the light of Neubauer's careful work. It was shown by Neubauer [18] that other agents besides epinephrin which act on the peripheral

[14] Dixon: Jour. Physiol., 1903, xxx, p. 97. Macfee: Jour. Physiol., 1903, xxx, p. 264.

[15] Schafer: Brit. Med. Jour., 1908, June 6, p. 1347.

[16] Hirayama: Zeit. f. exp. Path. u. Therap., 1911, 8, p. 649.

[17] Eppinger, Falta, and Rudinger: Zeit. f. klin. Med., 1908, 66, 1909, 67, 380.

[18] Neubauer: Biochem. Zeitschr., 1912, xliii, p. 335. It was noted by Cushing that chloretone prevents both *piqûre* and adrenalin diabetes.

blood-vessels and raise blood-pressure also induce glycosuria; barium chloride is an example. Here vaso-constriction and glycosuria are concomitant. On the other hand drugs of the narcotic group, for example, opium, chloral, and alcohol, which act on the central nervous system, often check or diminish the intensity of glycosuria following *piqûre*. These drugs produce this effect by an action opposite to that of epinephrin-vaso-motor paralysis and lowered blood-pressure. Neubauer has also noted that peripheral vaso-constriction is accompanied by hyperæmia of the liver. Now any procedure which induces hyperæmia along with stasis in the liver is apt to give rise to glucose excretion. These conditions of asphyxia appear to favor the transformation of hepatic glycogen into glucose.

EXPERIMENTAL PANCREATIC DIABETES

The work of von Mering and Minkowski [19] is now so well known that a review of it seems hardly necessary. The fact established and confirmed by many different investigators is that total ablation of the pancreas in animals causes a severe diabetes which is fatal. For a considerable period the glycosuria following this operation was by some, notably Pflüger,

[19] Von Mering and Minkowski: Zentralblatt f. klin. Med., 1889, 10, p. 393; Arch. f. exp. Path. u. Pharm., 1889, 26, p. 371. Minkowski: Untersuchung ü. d. Diabetes mellitus nach exstirpation d. Pancreas. Leipzig, 1893.

attributed not to the deprivation of the pancreas, but to the injury of nerves in the process of pancreatic removal. This objection was overcome by Minkowski,[20] who succeeded in transplanting small portions of pancreas under the skin of animals from which the pancreas had been removed. In these animals only a slight or no sugar excretion occurred; but if subsequently the transplanted portions were removed the usual diabetes ensued. Pancreatic tissue has been transplanted into the spleen with the same result.[21] Pflüger also opposed the idea of glycosuria resulting from removal of the pancreas because he noted that extirpation of the duodenum in frogs was followed by sugar excretion. Pflüger kept his frogs chilled following the operation, and this is prone to cause glucose excretion with frogs.[22] Von Mering removed the duodenum from dogs without any consequent diabetes.

If the pancreatic ducts be ligated there results an atrophy of the secreting cells. After months the only remnant of the gland left is a "thin film of opalescent tissue" composed mostly of the islands of Langerhans.[23] As a rule no diabetes develops in consequence

[20] Minkowski: Arch. f. exp. Path. u. Pharm., 1893, 31, p. 85. Hedon: Diabète pancreatique. Paris, 1908.

[21] Martina: Deutsch. med. Wochenschr., 1908, 34, p. 45.

[22] Rosenberg: Biochem. Zeitschr., 1909, XVIII, p. 95.

[23] Schulze: Arch f. mikr. Anat. u. Entwicklungs gesch., 1900, LVI, p. 491.

of this simple atrophy but takes place at once if the remnant be removed.[24] Pratt claims that there is a diminution in the assimilation limit for glucose with dogs following ligation of the ducts and atrophy of the pancreas. These experiments are all founded on those of Sandmeyer,[25] who in addition to ligating the pancreatic ducts removed a part of the gland and observed that diabetes developed after an interval. This last was the only experiment that appeared to Pflüger to be at all convincing of the pancreas' relation to glycosuria. The fact that impressed Pflüger was the gradual development of the glycosuria contemporaneously with the gradual atrophy of the pancreatic remnant. This is not what would be expected of a nerve injury and Pflüger [26] had contended that pancreatic removal was a nerve injury.

It is generally accepted to-day among physiologists that total removal of the pancreas causes a fatal diabetes. But how this is brought about is not decided. In the first place there is a hyperglycæmia and a rapid withdrawal of glycogen from the body. To account for the conditions von Mering and Min-

[24] Pratt: Arch. Int. Med., 1911, VII, p. 665. McCallum: Bull. Johns Hopkins Hospital, 1909, XX, p. 265.

[25] Sandmeyer: Zeitschr. f. Biol., 1895, XXXI, p. 12.

[26] See many papers by Pflüger in Arch f. d. ges. Physiol., 1907–1909. Pflüger's papers are worthy of study by every physician because they show what evidence is required to demonstrate an hypothesis. He draws the line black and clear between what may be and what is proved to be.

kowski offered two possible explanations: (1) The pancreas normally destroys some toxic or ferment substance; when the pancreas is removed this substance accumulates and causes sugar to be excreted. (2) Destruction of sugar in the body normally depends in some way on the pancreas; when the pancreas is removed sugar is no longer burned. The second hypothesis is the idea of an internal secretion although von Mering and Minkowski did not use that term in their early papers. Virchow [27] had conjectured years before that the pancreas had an internal secretion but he did not connect it with sugar metabolism. Among clinicians this conception had been held by Bouchardet, Frerichs, and Lancereaux in relation to sugar metabolism. Many experiments have been devised to demonstrate the presence in the blood of an internal secretion of the pancreas; among the earliest was Lépine's.[28] He attempted to show that the glycolytic power of the blood of an animal rapidly diminished after the pancreas is removed, but these claims were quickly undermined. The variations observed by Lépine were due to post-mortem changes in the blood.[29] Many other experiments with blood have promised much but have been unable to withstand searching

[27] "und das auch diese Druse nicht bloss nach aussen sondern auch nach innen in das Blut secernire." Virchow: Arch., 1854, 7, p. 580.

[28] Arch. med. Exper., 1891, p. 222.

[29] Kraus: Zeitschr. f. klin. Med., 1892, xxi, p. 315.

criticism. Among the most ingenious are those em-
pancreas normally destroys some toxic or ferment sub-
was devised by Sauerbruck and consists in uniting two animals so that there is a communication between the peritoneal cavities and an exchange of blood and lymph between the animals. It has been found that the parabiosis of a normal dog with one from which the pancreas has been removed results in either preventing or ameliorating the severity of the diabetes to a marked extent. The explanation offered is that the normal dog furnishes through the blood some substance which enables the depancreatized dog to utilize sugar.[30] This is possible but the experiments are not conclusive. As the vascular systems of the two dogs were in communication this alone would diminish the degree of hyperglycæmia of the depancreatized animal and that the sugar content of the normal dog's blood was raised is evidenced by occasional glycosuria. The normal dog may have stored up sugar as glycogen also. These and other objections that can be raised against the results of Forschbach's experiments make it doubtful if our knowledge has been increased by them.

Cohnheim's interpretation of his experiments,[31] had they been confirmed, would have added consider-

[30] Forschbach: Deutsch. med. Wochenschr., 1908, 39, p. 910; Arch. f. exp. Path. u. Pharm., 1909, 60, p. 121.

[31] Cohnheim: Zeit. f. physiol. Chem., 1903, 39, p. 336; 1904, 42, 401; 1905, 43, p. 547; 1906, 47, p. 253.

able evidence to support the hypothesis of an internal pancreatic secretion relative to carbohydrate metabolism. Cohnheim noted that when an extract of pancreas and muscle together are allowed to act upon glucose, part of the glucose disappears whereas either extract alone does not effect this destruction. The simple fact of the disappearance of sugar from these tissue extracts is pretty well attested by a number of chemists.[32] Interpretations have differed. There is now evidence that the glucose is not destroyed but is transformed, polymerized into higher carbohydrates.[33] It might be contended from these experiments that pancreatic activity is requisite for the storage of surplus sugar as glycogen, but this hypothesis would explain only post-prandial sugar excretion. There would be simply a diminution in tolerance for carbohydrate food. The hyperglycæmia of depancreatized animals during fasting is unexplained. While the gross effect on carbohydrate metabolism of removal of the pancreas is hardly questioned, an internal secretion which influences the destruction of glucose in the body has not been demonstrated by the experiments above mentioned. Hedon contended that the internal secretion of the pancreas must remain a pure hypothesis until it is possible to isolate from that

[32] Hall: Amer. Jour. Physiol., 1907, 18, p. 283.
[33] Levene and Meyer: Jour. Biol. Chem., 1911, 9, p. 97.

gland a substance which, administered to depancreatized dogs, will prevent the glycosuria. An extract of pancreas was made by Zülzer, who claimed that its administration prevented adrenal glycosuria. Zülzer [34] also believed that he observed favorable results in human diabetes following the use of his extract, but Forschbach [35] found the symptoms following the administration of such a nature that he considered the extract a dangerous medicament. It seems quite probable that Zülzer's results are due to the toxic action of the extract,[36] although there is the observation of Fugoni [37] that pancreatic extract destroys adrenal extract *in vitro,* which if true would give some basis for Zülzer's results. The latter investigator asserts on the basis of his experiments that glycosuria does not follow removal of the pancreas if the adrenals are also extirpated, and even when they are left intact but the veins ligated the glycosuria resulting from pancreatic removal is slight.[38] In view of the notable difficulty of complete pancreatectomy these experi-

[34] Zülzer: Berlin. klin. Wochenschr., 1907, 44, p. 474; Zeitschr. f. exper. Path. u. Therap., 1908, v, p. 307.

[35] Forschbach: Deutsch. med. Wochenschr., 1909, 35, p. 2053.

[36] Lymph and peptone both prevent adrenal glycosuria. Biedl. and Offer: Wien. klin. Wochenschr., 1907, 20, p. 1530. Glaessner and Pick: Zeit. f. exp. Path. u. Therap., 1909, 6, p. 313.

[37] Fugoni: Arch. ital. de Biol., 1908, 50, p. 209.

[38] Berlin. klin. Wochenschr., 1901, p. 1209; Deutsch. med. Wochenschr., 1908, 32, p. 1309.

ments require confirmation. If true they bring pancreatic diabetes within the range of the chromaffin system. Zülzer holds that pancreas diabetes is not primarily pancreatic but primarily adrenal in origin.

The conclusions of Zülzer are negated quite decisively by the experiments of Allen[39] whose work overthrows the frail structure of the polyglandular doctrine of diabetes.

There is some evidence which suggests that the inner secretion of the pancreas acts conjointly with the liver. In frogs Marceus found that no sugar is excreted after pancreatic removal if the liver is excised also. With higher animals removal of the liver is not compatible with life but the desired conditions have been approached by ligation of vessels and under these conditions but very scanty sugar excretion results. The difficulties surrounding the experiment preclude decisive results chiefly because of the short space of time that such experimental animals live. In this connection the work of Hedon is of interest. Pancreatic tissue transplanted into the carotid-jugular circulation does not prevent, according to this investigator, glycosuria in depancreatized dogs, but the sugar excretion sinks markedly when the pancreas tissue is implanted into the portal circulation.

[39] Allen, *loc. cit.*, p. 847. See also Lusk: Arch. Int. Med., 1914, XIII, 673.

Hedon [40] also found that serum from the blood of the pancreatic vein of a normal dog injected into the portal circulation of a depancreatized dog was followed by a dwindling of the glucose excretion almost to nil.

These various observations taken at their face value suggest that the internal secretion of the pancreas is of the nature of a hormone. The net result of all the experiments attempting to disclose an internal pancreatic secretion is: that while it has not been satisfactorily demonstrated it seems possible that such a secretion is elaborated and discharged into the blood. From what we know of internal secretions in general that of the pancreas probably does not produce its effect directly but acts rather with other enzymes in effecting the metabolism of glucose.

Several attempts have been made experimentally to disclose a relation between the pancreas and other organs of internal secretion. The ideas of Zülzer have already been referred to. Falta and his collaborators think that the thyroid is linked with pancreatic activity in the metabolism of sugar. Falta [41] claimed that adrenalin does not lead to sugar excretion with thyroidectomized dogs but this claim was refuted by careful experiments of Underhill [42] and by Grey.[43]

[40] Hedon: Compt. rend. Soc. Biol., 1911, 71, p. 124.
[41] Zeitschr. f. klin. Med., 1908, 66, p. 1; 1909, 68, p. 205.
[42] Amer. Jour. of Physiol., 1910, 27, p. 331.
[43] Jour. of Exp. Med., 1909, xi, p. 659.

This breaks an essential link in Falta's deductions which join the thyroid and adrenal in the causation of diabetes.

Falta's hypothesis and that of Zülzer are alike in so far as the mutual relations of pancreas and adrenal are concerned. The conception offered is that the secretion of the adrenal glands promotes the transformation of liver glycogen into glucose; the pancreatic function inhibits this transformation; pancreas and adrenal are antagonistic in their relation to glycogen transformation. If the pancreas be removed from an animal the inhibiting influence to glycogenolysis is lost and adrenal glycosuria results. It is a proper objection to interpose here that in no diabetic state, even when associated with increased blood-pressure, has there been demonstrated increased epinephrin in the blood. Again it is claimed in support of this theory that injections of extracts of pancreas prevent adrenalin glycosuria, but it has also been shown that many other tissue extracts prevent adrenalin glycosuria, so nothing specific for the pancreas can be claimed by that fact. It is difficult on examination to find adequate foundation for the basal conception of this doctrine. As an elaboration of this theory it is believed by the von Noorden school that the pancreas is under the control of the thyroid, which inhibits its action, and the thyroid in turn is influenced by the pituitary. The

whole elaborate mechanism is dominated by the nervous system through the vagus and sympathetic, which either promotes or inhibits the several glandular activities.[44] In criticism it may be acknowledged that isolated facts suggest on superficial consideration the relation of various glands with glycosuria, *e.g.*, acromegaly; but the establishment of so complex a doctrine as the one outlined is most difficult since it demands variations in experimental technic and the combined ablation of the two organs without which in some instances life can be supported only for the briefest periods.

PHLORHIZIN [45]

The glycosuria due to phlorhizin has been very thoroughly studied. From the time of its discovery by von Mering down to the present it has continued to engage the interest of physiologists, not because phlorhizin diabetes is in any way related to human diabetes but rather because by this means many problems in carbohydrate metabolism may be submitted to experimental test. In striking contrast to other forms of experimental glycosuria the blood in phlorhizinized

[44] For an exposition of these theories see von Noorden: Med. Klinik., 1911. VII, No. 1, p. 1, and a criticism of them. Minkowski: *ibid.*, 1911, VII, No. 27, p. 1031.

[45] For the complete literature see Lusk: Phlorhizin Diabetes, Ergebnisse d. Physiolog., 1912.

dogs contains less sugar than normal; there is a hypoglycæmia. It is generally assumed at present that the glucose excretion induced by phlorhizin is effected by action upon the kidney. This theory rests upon the experiment of Zuntz who injected in the renal artery of one kidney a solution of phlorhizin and observed that sugar was excreted from this kidney an appreciable time before it appeared in the urine from the other kidney. Minkowski believed that phlorhizin is broken up in the body into glucose and phloretin, the latter acts as a carrier of blood sugar to the kidney where the combination is broken up and the sugar excreted, while the phloretin is retained and combines with more blood sugar. There is a constant but slow excretion of this phloretin also, hence the effect of the initial dose slowly wears off. It seems doubtful, however, that the sole effect of phlorhizin is through the medium of the kidneys, since Grube noted [46] that in perfusing the livers of turtles more sugar was taken up by the perfusion fluid when it contained phlorhizin in addition to the other ingredients. This experiment would indicate that phlorhizin increases the breaking down of liver-glycogen into sugar, which is so rapidly excreted through the kidneys that it is not burned.

The results of the study of phlorhizin glycosuria have been already mentioned in connection with sugar

[46] Pflügers Arch., 1909, 128, p. 118.

metabolism. They require now only passing mention. It was noted by Lusk that in the first two or three days if dogs are kept under the influence of phlorhizin the sugar excretion is large but later this falls somewhat. This initial sugar excretion Lusk attributes to the removal of stored glycogen from the tissues. After the glycogen is removed there is a fairly constant relation of dextrose excretion to nitrogen excretion which is usually about 3.6 to 1. Lusk believes that in the thoroughly phlorhizinized dog no glucose is utilized, hence the dextrose-nitrogen ratio represents the maximum sugar derivable from protein. Since one gramme of nitrogen represents 6.25 grammes of protein the Lusk ratio would indicate that each 100 grammes of protein may yield 57 grammes of glucose, an amount considerably in excess of that indicated by the ratio in depancreatized dogs. The question arises in relation to phlorhizin diabetes: Is all the sugar from protein excreted in the urine or is a constant fraction catabolized? On the basis of their experiments Falta claimed that a ratio still higher than 3.6 could be secured by administering epinephrin to phlorhizinized dogs. The deductions that were drawn from these experiments are of no value since Ringer has conclusively shown that epinephrin is devoid of effect upon the ratio if the experimental animals have been completely freed of tissue glycogen. Moreover, in recent experi-

ments Lusk has found the respiratory quotient so low in completely phlorhizinized dogs that the combustion of carbohydrates seems excluded.

Phlorhizin glycosuria has been most productive of interesting results by furnishing a means of insight into the transformation of protein into sugar. Lusk has in this way disclosed that some of the amino-acids of which protein is composed are wholly transformed into sugar, while others are without effect on the sugar excretion. These amino-acids have already been referred to in considering the derivation of sugar from protein.

IV

ACIDOSIS

For the perfect performance of the chemical functions in the body it is necessary that the tissue fluids preserve a certain reaction. Normally there is a very small excess of potential alkaline over acid radicles. The blood is practically neutral. In the physiological processes there are constantly being formed as products of catabolism various acids which are either destroyed by further oxidation or are neutralized and excreted as salts and even when considerable quantities of mineral acids are ingested there is no appreciable change in the reaction of the blood and tissues. The body has in health sufficient reserves of alkalies to meet these ordinary demands. In morbid states, however, the accumulation of acid radicles may be very large and tax the defense mechanism of the organism to the utmost. The earliest manifestation of this excessive acid production is to be noted in the increased acidity of the urine. With many febrile states, for example, rheumatic fever, the urine is strongly acid and often persists so notwithstanding the ingestion of considerable amounts of alkalies. Strictly speaking the conditions where there is an excessive production of acids can be referred to as an acidosis. Under

these circumstances the production of acids does not necessarily lead to a predominance of acid radicles in the tissue fluids, since, besides the available sodium, potassium, and calcium, the organism furnishes ammonia on demand to combine with the acids and form neutral compounds. It is not demonstrated that the acid production accompanying fevers and allied conditions is so great as to give rise to clinical symptoms and the amounts of acids formed are relatively trivial compared with the excretion in diabetes mellitus.[1]

Since the acid in excess of amounts that are neutralized by the fixed bases combines with ammonia and is excreted as an ammonia salt it is evident that increased ammonia in the urine is a rough index of the degree of acidosis; the second test of acidosis is an increase in the acid radicles (H ions) over the alkaline (OH ions) in the blood. On account of the decrease in alkalies, the blood is less able to hold CO_2. There is then a decrease in the CO_2 content of the blood. These tests for a condition of acidosis have been found fulfilled in experimental conditions and are met with, in some degree, in diseases associated with acidosis.

In relation to diabetes the term acidosis was originally used by Naunyn to explain phenomena which

[1] For a discussion of these mild types of acidosis accompanying various diseases see Henderson: Amer. Jour. Physiol., 1908, 21, p. 427; Arch. Inter. Med., 1913, 12, pp. 146, 153.

were believed to be the result of accumulation of acids in the organism. Stadelman, a student of Naunyn, separated considerable quantities of β-oxybutyric acid from the urine of severe cases of diabetes [2] and recognized a similarity between the picture of diabetic coma and the experimental acid poisoning produced in animals by Walter. When 0.7 to 0.8 gramme of hydrochloric acid per kilo body weight is injected into the stomach of a rabbit there develops a loss of muscular power, rapid pulse, and a type of dyspnœa characterized by deep breathing and coma terminating in death. There is also observable in this condition a diminished alkalinity of the blood and a decrease in its content of CO_2. The CO_2 that could be extracted from the blood fell from 32 to 3 volumes per 100 volumes of blood. These experiments are the foundation of the Naunyn-Stadelman conception of diabetic coma as an acidosis. The amounts of acids separated from the urine by Stadelman were, however, insufficient to explain coma, and the theory rested upon insecure basis until Magnus-Levy [3] succeeded in recovering from the tissues of cases dead of diabetic coma amounts of acid which estimated in relation to body weight were greater than Walter used in his

[2] Stadelman at first believed this acid to be d-crotonic acid; it was identified as β-oxybutyric acid by Külz and by Minkowski.

[3] Magnus-Levy: Arch. f. exp. Path. u. Pharm., 1899, 42, p. 149; 1901, 45, p. 389.

experiments. Whether there is any other condition analogous to diabetic acidosis in that the accumulation of some acid in the body is responsible for clinical symptoms is at present doubtful; there is none where oxybutyric is the agent, none with such an enormous acid formation and excretion as in the diabetic state.

Ketonuria, that is, the excretion of β-oxybutyric acid, diacetic acid, and acetone in the urine, is not peculiar to diabetic acidosis. There is normally in the daily urine 50 to 60 milligrammes of acetone which is eliminated from the kidneys as diacetic acid, the transformation of diacetic acid into acetone taking place spontaneously. The expired air also contains a small amount of acetone which leaves the blood as diacetic acid. In measuring small amounts of the ketone bodies there is considerable technical error and the results for normal persons are variously estimated, but probably do not exceed 10 centigrammes per day.

The most important influence in increasing the ketone excretion is restriction of carbohydrate of the food. It has been repeatedly noted that in those conditions where the ingest of food or of starch is markedly diminished there results a ferric chloride reaction in the urine (Gerhardt's test). This is the explanation in great part of the acetonuria of fevers, of severe gastro-intestinal disease, and of cachexia. And from this the question at once arises as to what degree of

acidosis can be induced in normal persons by dietary restrictions. Hirschfeld, one of the first in the field of investigation, estimated only the acetone of which he recovered .44 gramme in the fifteenth day of a fat-protein diet. Magnus-Levy determined the total ketone bodies in his own urine while restricting the diet to meat and fat with the following results:

Day	Acetone	Oxy-butyric acid	Total ketone as oxy-butyric acid
1	0.07	0.40	0.52
2	0.24	0.94	1.37
3	0.45	2.10	2.9
4	0.75	3.4	4.75
5	0.90	4.4	6.02

In this experiment there was a daily dosage of 20 grammes of bicarbonate of soda, which has been shown to facilitate elimination of the acids formed. Benedict and Joslin [4] secured the excretion of 8.0 grammes of β-oxybutyric acid by the use of a carbohydrate-free diet with a normal man. While the formation and excretion of these amounts of ketone substances is suggestive it is comparable only to the milder cases of acidosis in disease. But Landergren and more recently Forssner [5] have secured much higher values. The latter working with himself as the experimental subject attained an elimination of 42 grammes of

[4] Metabolism in Severe Diabetes: Carnegie Institute, No. 170, p. 127.
[5] Skand: Arch. f. Physiol., 1909, 22, p. 349; 23, p. 305.

ketone bodies in one day, an amount comparable with many cases of very severe acidosis in diabetes. One other fact brought out in Forssner's work deserves special emphasis and that is that the ketonuria may persist even after the normal subject has ingested considerable carbohydrate; in one instance when 40 grammes of carbohydrate were ingested there was an elimination of 32 grammes of ketone bodies. It was also remarked that different individuals responded variously in their susceptibility to acidosis under diet restriction—a fact analogous to disease conditions. These experiments of Landergren and Forssner go very far in establishing the fact that acidosis is purely the effect of carbohydrate restriction. When it is recalled that the normal non-diabetic organism is never without some carbohydrate to burn—in the experiment mentioned 40 grammes [6]—the force of the argument is increased. It seems possible that if phlorhizin were used to prevent the combustion of sugar derived from protein there would result in a non-diabetic man an acidosis as severe as ever prevails in diabetic coma.[7] If then these experiments are trustworthy in

[6] Estimated from urinary nitrogen.

[7] This experiment has been recently made by my colleague, S. R. Benedict. A D : N ratio of 3.6 was secured. The $NH_3 - N$ amounted to over 4 grammes; β-oxybutyric acid, 32 gm.; diacetic acid, 5 gm. per day. In the experimental period of about two weeks over 300 gm. of β-oxybutyric acid was eliminated. The acidosis ceased promptly on discontinuing phlorhizin and ingesting sugar. Proc. Soc. Exp. Biol. and Med., 1914, XI, 134.

establishing as a fact that severe ketonuria is a consequence only of carbohydrate deprivation this fact would be strong evidence in support of the theory that oxybutyric and diacetic acids are normal links in the disintegration of higher fatty acids.

The theory that acidosis is a condition *sui generis* and is in some way peculiar to diabetes is worthy of examination. Von Noorden [8] had taken this position for the following reasons: (1) Some diabetics can absorb and oxidize 70 to 100 grammes of carbohydrate daily and still excrete 3 to 5 grammes of acetone. (2) Many diabetics develop ketonuria on changing from a mixed diet to one containing no carbohydrate, and the ketonuria persists when the mixed diet is again resumed. (3) In other cases the ketonuria usually resulting from strict diet is only temporary or absent. This can only be explained by supposing that the removal of all carbohydrate improves the general condition and alleviates the pathological state which produces ketonuria. Von Noorden cites a case of Satta's where the acetone bodies average 19 grammes on the first two days of strict diet; then gradually fell to 1.5 grammes on the eleventh to the thirteenth days, and four days later were down to 0.8 gramme. The sugar excretion on the first two strict diet days averaged 141 grammes, and fell to 114 grammes on the eleventh to thirteenth

[8] Metabolism and Practical Medicine. Chicago, 1907, vol. 3, p. 593.

days (that is, the patient in the latter period was burning 27 grammes of sugar more than at the commencement of the diet). (4) Patients of apparently the same physical condition and with the same severity of disorder may show wide variations in the degree of ketonuria. (5) Individual cases on the same diet exhibit variations in the amounts of ketone bodies excreted.

It is von Noorden's conception that under certain conditions the body can manufacture sugar from fat, and he conceives that the ketone bodies are in some way connected with this transformation. As we have already seen the origin of sugar from fat is absolutely undemonstrated.

When we examine von Noorden's reasons for considering diabetic acidosis as a departure from normal in relations "not merely quantitative but qualitative and fundamental," we must admit at once that not in all respects at present are the normal relations entirely clear. Individuals differ, as Forssner determined, in the amount of carbohydrate requisite by combustion to inhibit ketonuria. It was noted above that some normal persons still excreted ketone bodies in large amounts when ingesting 40 grammes of carbohydrate. So that the variability of the disease state is not peculiar, as von Noorden believes. The fact that some diabetics first develop ketonuria with a carbohydrate

free diet or that a slight ketonuria may become severe is well recognized. There are severe cases where the amount of sugar utilized is small and the margin narrow, and when the ketonuria persists after additions of starch to the diet it is usually found, if looked for, that this carbohydrate is not utilized. In other words the tolerance has become slightly less—probably just enough less to induce a persistent acid formation. With those individuals where the ketone excretion falls during a period of carbohydrate-free diet (Satta's case) it is observable in every case where the data are sufficient for evidence that there is a gradual and parallel fall in the dextrose elimination; *i.e.*, a rise in tolerance, which means more sugar is burned in the body. In Satta's case cited above, the difference amounts to 27 grammes, which could easily effect the change, since this amount was not all the sugar burned, but represented an addition to the daily amount consumed at the commencement of the diet period. The peculiarities claimed by von Noorden for the acidosis of diabetes, then, offer no insurmountable obstacle to the current theory; since all the conditions are either simulated or approximated in the healthy body by restrictions and changes in diet. If, on the other hand, it can be shown that metabolism during fasting or with a diet devoid of carbohydrate is wholly or in part pathological, then there is basis for the conception of

acidosis as a perversion rather than a result of incomplete normal process. There is no direct evidence on this question but considerable that applies indirectly.

Normal man may ingest fifteen to twenty grammes of β-oxybutyric acid and only traces reappear in the urine; on the other hand, if diacetic be fed there results an excretion of β-oxybutyric acid.[9] When either diacetic or β-oxybutyric acid is given alone to cases of severe diabetes both ketones appear in the urine.[10] This discrepancy at once suggests some essential change in the diabetic organism which will be considered subsequently. The subject of acidosis has not received much attention in experimental diabetes, but with phlorhizinized dogs there are considerable quantities of ketone bodies recoverable from the urine in spite of the fact that carnivorous animals are not so prone to ketonuria as man. Here again the phenomenon is concomitant with failure of carbohydrate combustion. The livers of depancreatized or phlorhizinized dogs yield more diacetic acid in perfusing them than normal organs. Embden [11] found that normally from 12 to 27 milligrammes of diacetic acid was recoverable from a litre of perfused blood, while with diabetic dogs he found 70 to 130 milligrammes of

[9] Blum: Münch. med. Wochenschr., 1910, 57, No. 13, p. 683.

[10] Neubauer: Verhandl. d. deutsch. Kong. f. inn. Med., 1910, 27, pp. 566–574.

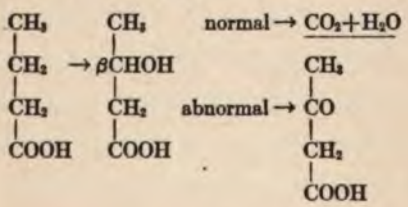
[11] Embden: Biochem. Zeitschr., 1908, 13, p. 262.

diacetic acid. The extracts of tissues had not, however, lost their power of destroying the ketone bodies.

Now if it be assumed that the ketone bodies result from an incomplete oxidation of fatty acids which normally progresses to CO_2 and H_2O there must be some hypothesis as to the stage at which this hindrance to normal metabolism occurs in order to explain the appearance of two intermediary products: β-oxybutyric and diacetic acids. It is quite generally agreed that when butyric acid enters the diabetic organism both β-oxybutyric and diacetic acids appear in the urine; while under normal physiological conditions all three of these substances undergo complete combustion. It might be assumed that there is in severe diabetes either (1) a defect in the cleavage of β-oxybutyric acid or (2) a hindrance to the oxidation of diacetic acid. In Neubauer's opinion it is unlikely that processes so essentially different should always be involved together. He found on examining the results of urine analyses for ketone bodies that the β-oxybutyric occurred quite constantly as 60 to 80 per cent. of the total ketone bodies. From this fact it is suggested that there is a state of equilibrium in the tissues between diacetic and β-oxybutyric acids, and this equilibrium is the characteristic state for a reversible reaction; according to current theories

$$C_3H_7OCOOH \rightleftarrows C_3H_5OCOOH$$

The reaction runs normally from left to right but in grave cases of diabetes there arises a difficulty in diacetic destruction in consequence of which this substance accumulates and the reversed reaction occurs from right to left. In order to test this hypothesis (that diacetic acid may go over into β-oxybutyric) Neubauer [12] gave large amounts of diacetic acid (30 grammes) as the sodium salt to cases of severe diabetes and observed a rise in both ketone bodies in the urine. The most probable process for the disintegration of the fatty acids in health is through β-oxybutyric acid to CO_2 and water without the intervening production of diacetic acid. In severe diabetes or carbohydrate starvation a false process is initiated in the oxidation of oxybutyric acid to diacetic. This in turn gives origin to the state of equilibrium and reversible reaction.



Dakin [13] has shown that liver tissue may not only oxidize β-oxybutyric acid to aceto-acid, but also reduce

[12] Neubauer: Verhandl. d. deutsch. Kong. f. inn. Med., 1910, 27, pp. 566–574.

[13] Jour. Biol. Chem., 1910, 8, p. 97.

diacetic to β-oxybutyric acid; the reaction effected depending among other conditions on the oxygen supply.

$$CH_3.COHO.CH_2.COOH \underset{\text{reductase}}{\overset{\text{oxidase}}{\rightleftharpoons}} CH_3.CO.CH_2.COOH$$

Blum[14] believes the normal path for the catabolism of butyric acid is by way of diacetic acid without the formation of β-oxybutyric acid as an intermediate step. His experimental results do not justify so wide a generalization. This explanation would clarify why normal persons, in contrast to severe diabetics, may ingest large quantities of oxybutyric acid without excreting diacetic acid in the urine, but diacetic may lead to some oxybutyric excretion. From this point of view β-oxybutyric acid is the only one of the ketone bodies that is not an intermediary product in normal catabolism.

It is not possible at present to give any satisfactory answer to the question why the withdrawal of carbohydrates from the diet induces an acidosis. It has been suggested already that this deprivation in man may institute an entirely pathological type of metabolism, but the only evidence for this is the relative failure of carnivorous animals (dog) to develop ketonuria during fasting. Scarcely more satisfactory is Geelmuyden's assumption of a synthesis be-

[14] Münch. med. Wochenschr., 1910, 57, p. 683.

tween the ketone bodies and sugar as necessary for oxidation of the latter. If sugars are not burned the ketones are not; which is, after all, only a restatement of "Das Fat verbrennt im Feuer der Kohlehydrat." This doubtless expresses the effect, but hardly the mode of operation. It has also been conjectured that since fat in the diet influences ketonuria, acidosis is in some way interlinked with the mobilization of fat in the body during starvation and as evidence for this is cited the lipæmia and the fatty liver of diabetic coma.

The evidence at present available indicates that (1) ketonuria is a result of carbohydrate deprivation. This deprivation is in effect the same whether the carbohydrate is not ingested or is ingested and not burned. There is no essential difference between the ketonuria of sugar-starvation and severe diabetes. (2) The excretion of β-oxybutyric acid indicates an incomplete normal catabolism.

THE MOTHER SUBSTANCES OF THE KETONE BODIES

The natural inference made by the older investigators that the ketone bodies are products of abnormal carbohydrate catabolism is no longer believed. As soon as it was recognized that it is in just those cases where least sugar is burned that the acid formation is greatest, it then became apparent that one must look either to protein or fat for the precursors of oxybutyric

acid. An increased excretion of ketone bodies following the ingestion of butter was attributed by Geelmuyden to the lower fatty acids contained in butter, and not until the studies of Magnus-Levy [15] disclosed the enormous formation of ketones that may occur was it appreciated that all fatty acids must contribute to make up so large a sum. Refinements in methods of investigation have led to quite definite information as to the various organic complexes which may be transformed into the ketone bodies. The methods chiefly employed have been (1) the administration of the substance to be tested to diabetic patients under rigidly controlled conditions of experiment and the result noted in the urinary ketone excretion. (2) The perfusion of dogs' liver with defibrinated blood to which is added the substance for test and the total ketone in the blood determined before and after perfusion. (3) Administering to dogs poisoned with phlorhizin the substance to be tested. By these methods a very large number of fatty acids and amino-acids have been investigated. A list of the more important is noted in the accompanying table.[16] It is of interest that many

[15] In one case there were excreted in the urine in three days 342 grammes of β-oxybutyric acid and diacetic acid, with nitrogen equivalent to 271 grammes metabolized protein from which about 120 grammes of sugar were derived. Joslin has reported similar studies. Magnus-Levy: *loc. cit.*

[16] Dakin: Jour. Biol. Chem., 1913, 14, No. 3.

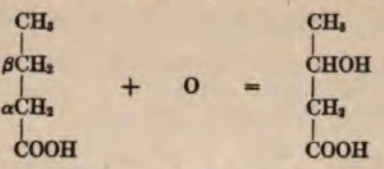
of the protein derivatives that are not ketone precursors are transformed into sugar as has been previously pointed out. The notable fact observed in the table of fatty acids is that those with an even number of carbon atoms in the molecule break down into ketone bodies while those with an odd number of carbon atoms do not. The reason for this becomes apparent in consideration of the mode of oxidation of fatty acids in general.

	KETOGENIC		
Fatty acids	Perfusion liver	Human diabetes	Glucogenic
Propionic (C_2H_5COOH)	−	−	+
Butyric (C_3H_7COOH)	+	+	..
Valerianic (C_4H_9COOH)	..	..	+
Caproic ($C_5H_{11}COOH$)	+	+	..
Heptylic ($C_6H_{13}COOH$)	..	..	+
Octoic ($C_7H_{15}COOH$)	+	..	..
Nonoic ($C_8H_{17}COOH$)	−	..	..
Decoic ($C_9H_{19}COOH$)	+	..	..
Palmitic ($C_{15}H_{31}COOH$)	+	..	..
Stearic ($C_{17}H_{35}COOH$)	+	..	..
Oleic ($C_{17}H_{34}COOH$)	+	+	..
Amino acids			
Alanine	..	..	+
Arginine	..	..	+
Aspartic acid	..	..	+
Cystein	..	..	+
Glutamic acid	..	..	+
Histidine	(?)	..	(?)
Leucine	..	+	..
Lysine	(?)	..	(?)
Phenylalanine	+	+	..
Tyrosine	+	+	..

By an elaborate series of experiments Knoop [17] has shown that when oxygen is united to the fatty acid molecule in the body this union occurs with the β-car-

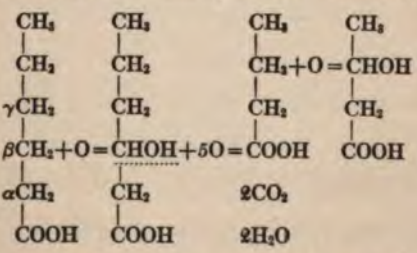
[17] Knoop: Beitr. z. chem. Physiol. u. Path., 1904, 6, 150.

bon atom. In the case of butyric acid it is evident that simple oxidation transforms it into β-oxybutyric acid.



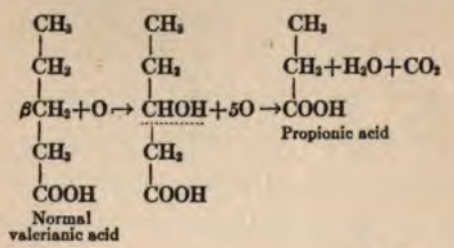
The same reaction takes place with acids containing a large number of carbon atoms; first an oxidation in the beta position, then in consequence of further oxidation a split in the chain between the alpha and beta atoms with the formation of an acid containing two less carbon atoms and CO_2 and H_2O. In this manner the higher fatty acids are disintegrated to the lower, losing two atoms of carbon by each oxidation. Thus it becomes clear why only fatty acids with an even number of carbon atoms produce butyric acid.

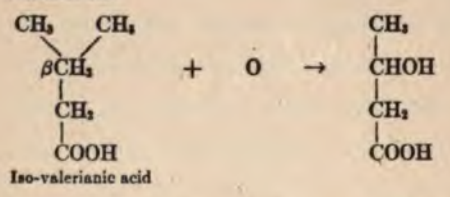
The position of the atom is reckoned from the COOH group thus in caproic acid ($C_5H_{11}COOH$), and the reaction is an example of β-oxidation.



In presenting the theory of beta-oxidation reference has been made to the straight chain fatty acids

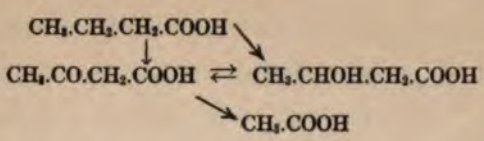
only. Acids with branched chains behave somewhat differently. Normal valerianic ($C_5H_{10}O_2$) acid is not ketogenic, iso-valerianic acid is ketogenic. The reactions for each may be written as follows:





Also it is apparent that only one molecule of butyric acid can be derived from each molecule of a higher fatty acid. Fatty acids with an uneven number of carbon atoms are not found in the fats of the animal body. Butyric acid may be derived then from all the fats of the tissues and food.

From the results of experiments with butyric acid it can hardly be doubted that oxidation takes place with the formation of diacetic acid primarily and that the β-hydroxybutyric acid is secondary to a reduction of the diacetic. The possible results may be represented as follows:

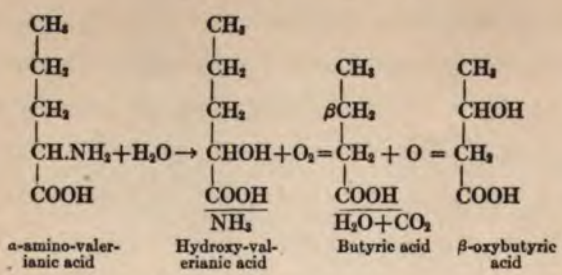


It is not possible to be in the least dogmatic regarding the pathological steps until our knowledge of the normal is more complete.[18]

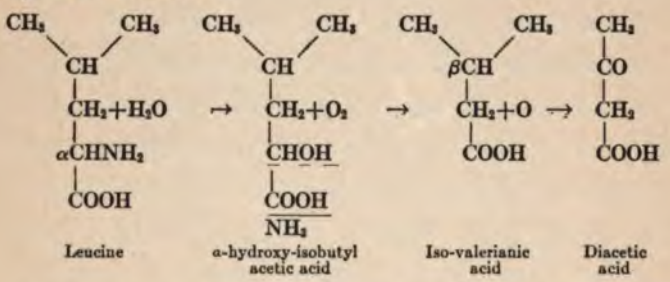
Since, however, but one molecule of butyric acid can proceed from a given fatty acid there is a practical advantage to the diabetic with acidosis in using a higher fat rather than a lower. For example, in butter the butyric acid is at once converted by the first oxidation into oxybutyric acid and very little energy is liberated in this transformation, whereas with the higher fatty acids there is a succession of oxidative steps each liberating energy before the butyric is finally derived.

In the transformation of amino-acids, the cleavage products of protein, into ketone bodies there is no departure from the principles already set forth. The presence of the amino group (NH_2) determines in the first instance to which carbon atom the oxygen is joined and hence the position of the initial cleavage in the molecule; thence the reaction proceeds as already detailed.

[18] For a concise presentation of the chemical aspects of fatty acid oxidation see Dakin: Oxidations and Reductions in the Animal Body. New York, 1912.



The reaction for leucine (α amino-isobutyl acetic acid) is as follows:



The relative amounts of ketone bodies in the urine derivable from protein and fat respectively cannot be definitely stated, but as only a few of the amino-acids composing protein are convertible into ketones the amount from this source is probably small. The predominant factor is the fat.[19]

Are then the ketone bodies to be regarded as products of normal metabolism which in consequence of some cellular disturbance have escaped the final steps of disintegration? The perfusion experiments of

[19] If all the fatty acid were converted to β-oxybutyric acid, 100 grammes of fat would yield 36 grammes; 100 grammes of protein probably not over 20 grammes.

Embden would indicate this to be the case, qualitatively at least, since it is hardly probable that the conditions of their experiment institute an activity in the liver that is wholly pathological. Nor is it inconceivable that the large amounts of β-oxybutyric acid excreted in the urine by patients in diabetic coma, 100 to 150 grammes per day, could be under normal conditions completely burned. Normal dogs can metabolize 2 to 3 grammes of β-oxybutyric acid per kilo body weight per day and of diacetic acid much more. If then it be assumed, as many believe, that the ketone bodies represent only interrupted oxidation, at what step does this disturbance occur? It has been shown that either aceto-acetic or β-hydroxybutyric acids are logical links in the oxidation of fatty acids; and it seems quite probable that each is formed from different precursors and as soon as formed undergoes oxidation to lower fatty acids, such as acetic and formic.

$$CH_3.CO.CH_2.COOH + H_2O = CH_3.COOH + CH_2.COOH$$
$$CH_3.CHOH.CH_2.COOH + O = CH_3.COOH + CH_2.COOH$$

Under these circumstances, only when conditions for oxidation failed would these acids accumulate and approach a state for equilibrium of transformation one to the other.

In the course of testing various substances to determine whether they may be transformed into ketone bodies it was noted that some substances inhibit ketone

formation in perfusion experiments and in the diabetic organism. This class of compounds is spoken of as antiketogenic. Chief among these substances, at least for the normal organism, are the carbohydrates and, as Hirschfeld demonstrated, also protein when it is ingested in large amounts. In one experiment a marked ketonuria incident to an exclusively protein diet which was equivalent to from 20 to 27 grammes nitrogen per day, vanished when the ingest was increased up to 30 to 40 grammes of nitrogen.

In the experiments conducted by perfusing liver, with diabetic men and with phlorhizinized dogs the results secured are not always clear cut nor concordant. Of the amino-acids, glycocoll, alanine, glutamic and aspartic acids are antiketogenic (Baer and Blum,[20] Borschardt), possibly because they may be transformed into sugar; the results with acetic and lactic acids are conflicting.

With diabetic patients Neubauer[21] has shown a decided reduction in the urinary ketone bodies following the ingestion of alcohol.

		Alcohol		
	1st day	2d day	3d day	4th day
Acetone	1.08	0.58	0.91	2.4
β-oxybutyric	6.90	2.50	3.10	8.2

Hirschfeld found no change in the urine of a normal man after the use of alcohol.

[20] Baer and Blum: Hofm. Beitr., 1907, 10, p. 80; 11, p. 101.
[21] Neubauer: Münch. med. Wochenschr., 1906, 53, p. 791.

Of the other substances that influence the acid production in normal persons many are not of use with diabetics or the observed results have not been uniform. Glycocoll is clearly antiketogenic in some instances (Hirschfeld), but large amounts are required, 40 to 60 grammes. With xylose, inosite, citric acid, and glucosamine the effect is not definite. Those substances which are most efficient in reducing the ketonuria of normal persons, carbohydrates and protein (since it is converted into sugar in the organism) are of no effect with severe diabetes, while on the other hand, alcohol which is inoperative with normal man is antiketogenic with many severe diabetics.

V

PATHOGENESIS

THE immediate cause of glycosuria may be either (1) an increased permeability of the kidney to normal concentrations of sugar in the blood, (2) the blood sugar may be so changed in its physiochemical state that it passes through the renal filter, or (3) the blood sugar may be increased above the powers of the kidney to retain it.

The first condition is that of renal diabetes in which the blood sugar is normal. It is supposed at present that the glycosuria here depends upon an abnormal permeability of the kidney to the sugar in the blood. The peculiarities of renal diabetes are discussed elsewhere. It seems possible that there is also a renal element in true diabetes, since the glycosuria is often of a more pronounced degree than is explicable by the hyperglycæmia. With non-diabetics the increase in the blood sugar attendant upon fever is but seldom manifested in glycosuria. On the other hand, many diabetics excrete sugar at times when the blood sugar is very slightly, if any, above the normal bounds. This is the evidence commonly cited in favor of a renal element in true diabetes. The glycosuria under these conditions can be explained as well by assuming a

change in the state of the blood sugar as by postulating an increase in renal permeability. This doctrine is based upon the idea that the blood sugar normally exists in some combined state with either protein, a lipoid, or some such substance; and in consequence of this combination there is no diffusion normally through the renal epithelium. In the diabetic the sugar is assumed to be uncombined and hence diffusible. In other words, normally the sugar exists in a colloidal state, in diabetes as a crystalloid. This conception is not new and in one form or another has been supported by the majority of students of diabetes. What then is the objection that may be brought against the hypothesis? Simply that the combined state cannot be demonstrated. The careful and well planned experiments of Rona failed to indicate either by methods of dialysis or by using collodial precipitants that the blood sugar is combined. As there are inherent objections to any known physicochemical means for the solution of the problem because of the possible delicacy of equilibrium of the substances in blood, the possibility still remains that the normal blood sugar exists in a colloidal state. When considerable amounts of sugar are given to normal animals or man, either by mouth or subcutaneously, there is no diuresis even though some sugar be secreted into the urine, while with diabetes there is a diuresis proportionate to

the sugar loss. Diuresis also results from introducing sugar solutions directly into the circulation of normal animals, and from these facts Allen [1] concludes that the blood sugar is normally in a combined state. The hypothesis is alluring but cannot be subscribed to on the facts at present available.

The third possible cause of glycosuria, increase in the amount of blood sugar, is observed with the great majority of diabetics and this increase has generally been conceived as the immediate occasion for sugar excretion in the urine. This increase is often of a degree that could hardly be retained by a normal kidney and it is not then necessary to postulate an increase of renal permeability. What then are the causes of the hyperglycæmia? There are three which appear possible: (1) Overproduction of sugar, (2) failure to warehouse sugar that is formed, (3) failure of the cells to utilize sugar.

The overproduction of glucose takes place in some of the experimental glycosurias, notably with *piqûre,* and is dependent upon the glycogen deposits in the body. If there is no glycogen available there is no resultant hyperglycæmia nor glycosuria and the latter ceases when the glycogen is exhausted. Conceivably the glycosurias following injuries, *i.e.,* fracture of the skull, are of this nature. Von Noorden has expressed

[1] Glycosuria, p. 303.

the opinion that overproduction or abnormal production is a large factor in the diabetic state. For this doctrine there is no basis, since all the sugar excreted is readily accounted for. Other than glycogen the only known source of sugar in the body is protein and all evidence goes to show that the glucose production from protein is normally at its maximum. For von Noorden's belief in the transformation of fatty acids into sugar there is no evidence. Hence there can be no overproduction of sugar in a qualitative sense. If the substances which form sugar undergo this change more rapidly in the diabetic organism than in health (if the overproduction is purely quantitative), then the fact would be disclosed in other metabolic relations (*i.e.*, nitrogen metabolism), which is not the case. It matters not whether the stimulus come to the liver direct or, as von Noorden believes, through a complex relation of the chromaffin system, the hyperglycæmia depending on liver deposits must fall when these deposits are diminished as in severe diabetes. In these very instances the sugar output is largest and the ability to store glycogen most impaired.

The overproduction theory of diabetes of the von Noorden school rests to a large extent on the experiments of Porges and Salomon [2] who found that ligation of the abdominal aorta and inferior vena cava in

[2] Biochem. Zeit., 1910, xxvii, pp. 131, 143.

rabbits and depancreatized dogs causes a rise in the respiratory quotient. They interpreted this to indicate that (1) the organism depends on the liver for ability to burn protein and fat, and (2) depancreatized animals retain the power to burn sugar. Murlin [3] has shown that under the conditions of the above experiment the changes in respiratory quotient are due to changes in the mechanical factors of circulation and that the metabolism is not changed.

The severe diabetic manifests a failure both to warehouse sugar and to utilize sugar. Normally, ingested sugar is stored either as glycogen or as fat and the ability to do this is practically unlimited. Even when very large amounts of glucose are ingested and there is an escape of some into the urine the amount lost is but a small fraction of the total ingested. And this may be continued indefinitely; indeed, with those individuals who indulge excessively in starchy and sweet foods, is continued for years, illustrating thereby the ability of the healthy organism to store up surplus carbohydrate. On the other hand, where sugar is ingested by persons with severe diabetes it is excreted quantitatively in the urine. There is neither ability to store this sugar as glycogen and fat nor to utilize it for energy. That the ability to utilize glucose is lost is also disclosed by the respiratory quo-

[3] Jour. Biol. Chem., 1913, 16, p. 79.

tient[4] which with these cases is low, indicating the combustion of protein and fat. Failure of the cells to make use of the sugar presented to them is equivalent in effect to starvation. Normally when the organism requires sugar there is a responding production in sugar formation from the glycogen stores and this formation continues so long as there is demand. In diabetes the demand is continuous from the cells and because there is no utilization and a constant demand the blood sugar rises. In this sense and this only is there any overproduction of sugar.

Finally, why is the diabetic organism unable to utilize carbohydrate? Evidently this is not an impairment of oxidation, since in this respect the diabetic appears normal. Several theories have been advanced but the question is yet open. Here again the question reverts primarily to the state of the blood sugar. The older conception postulated an abnormal combination of the blood sugar in consequence of which the cells were not able to become " fixed " to the sugar (Schmiedeburg, Seegen, Naunyn). As a result of the pancreatic theory of diabetes Minkowski saw two possible actions of an internal secretion: (1) action on the sugar preparing it for cleavage; (2)

[4] When sugar is administered to depancreatized dogs the respiratory quotient does not rise as it does with normal dogs, indicating that the sugar is not burned; Veyzar and Fejes: Biochem. Zeitschr., 1913, 53, 140; Murlin and Kramer: Jour. Biol. Chem., 1913, xv, 365.

action on the cells. A third hypothesis has been advocated; namely, that an antagonistic substance is normally destroyed by the pancreatic internal secretion (toxic theory). In diabetes the pancreas fails to effect destruction and as a result combustion of sugar is inhibited. These ideas are based upon a conception of blood sugar normally, in some combination; pathologically, free or joined in an abnormal compound. The most insistent advocate of this doctrine was Pavy.

The recent application of Ehrlich's side-chain theory to the whole domain of cell activities has found its expression in relation to diabetes in Allen's hypothesis of a pancreatic amboceptor. The Ehrlich conception of the utilization of foods by the cells is that the nutrient material must first become fixed to the cell before it can be oxidized in the same manner as the complement is fixed to the cells through the mediation of an amboceptor. The application of the theory to diabetes supposes an amboceptor normally supplied by the pancreas to be lacking in the disease state and in default of amboceptor the cells are unable to "fix" and to utilize sugar.

No theory thus far advanced is adequate to explain all the phenomena observed with human diabetes, nor does any theory at present rest on a broad basis of demonstrated fact. These hypotheses must be held purely in the scientific spirit of a working basis for experiment.

VI

HISTORY

THE earliest reference that may be construed as alluding to diabetes is the polyuria mentioned in the papyrus Ebers. Celsus speaks of a disorder remarkable for the increase in the amount of urine and leading to emaciation. It seems rather surprising that a disease so clearly defined made no recordable impression on the Greeks, yet no mention is found in the texts that have come down to us earlier than the writings of Aretæus, 150 A.D. Like Galen, his contemporary, he dwells upon the polyuria and the abnormal thirst. Aretæus first gave the name "diabetes" (*διαβαίνειν*) to the disorder on account of his conception of the disease as a transudation of the liquid ingesta and fluids of the body into the urine. To the kidneys Galen assigned the cause of abnormal diuresis (diarrhœa per urinas) and this view prevailed throughout the middle ages. A somewhat different interpretion of the disease was given by Paracelsus in attributing to an abnormal salt formation the causes of renal activity. This notion of a morbid state of the blood was enlarged upon independently by Sylvius, father of the iatrochemical school (*Opera med.*, Amstelodami, 1680).

Until the latter part of the seventeenth century European physicians never suspected that the urine in this disease contained sugar. If it were not then for the other characteristic symptoms referred to in the earlier writings we should be left in doubt whether the disorder described were diabetes *mellitus* or *insipidus*. But according to the Ayur Veda (500 A.D.) the saccharine nature of diabetic urine had been known to Hindu physicians from remote times, and undoubtedly diabetes mellitus is alluded to in the fifth century in the description of a disease characterized by "honey urine." European medicine was enlightened by Willis in 1674, and from then on diabetes was differentiated as saccharine, and non-saccharine; but not till a century later was sugar demonstrated in the urine by Dobson and the disease recognized as a clinical entity. Dobson conjectured that the blood of diabetic patients contains sugar and Rollo concurred in this supposition by reason of the diminished tendency to putrefaction. Many chemists made fruitless attempts to detect blood sugar, which was finally demonstrated by an apothecary, Ambrosian, in 1835. Instead of elucidating the cause of the disorder, these new facts, even as to-day, made the essential cause but more vague and intangible. Many and curious theories were advanced, flourished for a day, and were forgotten. Some believed the fault to be essentially digestive in that the starchy

foods are too rapidly converted into sugar (Bouchardat), while others recognized the cause in a diminished alkalinity of the blood. No theory had a basis until Claude Bernard published his experiments upon the relation of the liver to sugar formation (1848) and upon *piqûre* glycosuria (1850). These experiments of Bernard opened up paths of investigation which are yet being followed by physiologists and pathologists.

Proportionate to the scientific knowledge of diabetes its therapy was precocious. Shortly after Dobson demonstrated sugar in diabetic urine another Englishman, John Rollo, pointed out the deleterious effects of carbohydrate diet. Rollo introduced the meat diet in the treatment of diabetes and the results observed by this method influenced at the time, to no little degree, the pathological theories of the disorder. No important advances were made upon Rollo's method until the latter part of the last century.

That severe cases of diabetes were liable to die in a peculiar form of coma has been known for more than a century, but to Kussmaul (1877) in Germany and to Sir Walter Foster in England we owe a careful description of its features.

VII

ETIOLOGY

THE incidence of diabetes as estimated by mean mortality statistics indicates that the disease is not common. For those countries of western Europe wherein vital statistics are most carefully recorded, there are annually five deaths from diabetes per 100,000 population. The registration area of the United States and the larger cities indicates an annual mean mortality of 12.6 per 100,000 living persons. Within these areas, however, there is noted a great variation in the figures which is most striking in comparing large cities. In Helsingfors the average is 5, while in Copenhagen it is 15; in Berlin 20, Paris 14, London 7. The lowest mortality per 100,000 population appears to be in Hong Kong, 0.15, and the highest in Malta, 37.8. Within the United States the mortality in the larger cities varies widely; in Boston it is 16.1; Chicago, 11.1; [1] New Orleans, 8.5; New York, 15.1; [1] St. Louis, 12.9; San Francisco, 15.[1] These figures can hardly be taken at face value, due to the inherent defects in all modes of classification. It is probable, however, that the frequency of the disease is under- rather than overrated; many cases doubtless

[1] Data kindly furnished by the Health Officers of these cities.

escape detection in the absence of urine examinations. Taken roughly these statistics may indicate the frequency of diabetes in large masses of population. It is the belief of some authors that diabetes is becoming more frequent and the cause assigned for this is the increase of wealth and consequent indulgence to the palate. It cannot be overlooked that methods of diagnosis are becoming all the time more generally used than heretofore, and that diseases are now detected where formerly no diagnosis was attempted. An increase in the frequency of many maladies might be cited where the explanation is solely that a diagnosis is made. It is possible, as some assert, that diabetes is more frequent than half a century ago but better evidence is required to establish the fact.

It has long been a tradition that certain races are more susceptible than others to this disease, and the Jews are commonly cited as an example. Of 400 cases in Frerichs' series, 102 were Jews. The susceptibility of the Hebrews is best attested by the careful survey of Frankfurt a.M. by Wallach [2] who found that the proportion of deaths from diabetes to the total deaths from all other causes was six times greater among the Jews than among the other inhabitants. It was shown also that the mortality [3] from diabetes among the Jews

[2] Deut. med. Wochenschr., 1893.
[3] Williamson: Diabetes Mellitus, London, 1898, p. 100.

was greater at all ages. Likewise the Hindus in India are said to suffer more from the malady than the other races. In America most authors agree that relatively few cases are found among the colored race. This statement is not demonstrable by available statistics. The vital statistics of the United States Government show the frequency of diabetes as a cause of death in the white and colored races per 100,000 population as abstracted for three of the states.

Connecticut.....19.9 white, 6.0 colored.
Maryland.....14.4 white, 4.7 colored.
Michigan.....14.8 white, 12.0 colored.

The available statistics in America and particularly in Europe leave but little room for doubt that social status is an important factor in the incidence of diabetes. It is particularly among the well-to-do classes that the highest percentages of cases are found. Even with Hebrews it is chiefly the rich who are afflicted; among the poor there is usually only a slightly increased percentage over the other members of a community. Bertillon [4] has shown that the mortality from diabetes in Paris is higher in all those *arrondissements* where the inhabitants are wealthy. It is not easy to select, out of the possible causes that riches may contribute, the important factor; besides overin-

[4] Bertillon: De la frequence des principales maladies á Paris pendant la periode 1865–1887, Paris, 1889.

dulgence in foods, the wealthy man often takes too little exercise, and very often he carries large responsibilities which entail constant nervous tension. The fact that women are somewhat less disposed to diabetes than men suggests, perhaps, the importance of the nervous strain of modern city life as a contributing cause, especially among the rich. According to the United States Census mortality statistics of the 140 classified occupations, the percentage of deaths due to diabetes is highest among lawyers, clergymen, and commercial travellers.

An inherited predisposition to diabetes is well attested by a number of remarkable cases recorded in the literature. Morton first called attention to this fact in 1696. Von Noorden and Pleasants [5] have each recorded a family in which one or more members in each generation were affected. There are also a number of instances where two or more children in a family have succumbed to diabetes. I have reported a family of four children all of whom became diabetic between the ages of six and seventeen years.[6] In an analysis of cases of this kind there is not always a history of diabetes in the parents; it is often noted, however, that there is a neuropathic taint in the family. Naunyn

[5] Von Noorden: Zuckerkrankheit, Berlin, 1907, p. 45. Pleasants: Johns Hopkins Hospital Bulletin, 1900, 11, p. 325.

[6] Foster: Johns Hopkins Hospital Bulletin, 1912, 23, p. 54.

took especial care to secure data and found that in 31 per cent. of 201 cases there was a history of diabetes in some relative. Fritz and Joslin observed this fact in 23.8 per cent. of their cases. An inherited tendency was noted by Lion[7] in 62 per cent. of 18 diabetic children where the family history was known.

A curious hereditary relation which diabetes mellitus sometimes bears to diabetes insipidus should be mentioned. Diabetes mellitus in a parent and diabetes insipidus in one of the children was reported by Senator;[8] and there are a few cases recorded where diabetes insipidus has occurred in some member of a diabetic family. The relation of the two diseases is further suggested by non-saccharine diabetes being succeeded by glycosuria. Some of these cases are supposed to have regained perfect health.

Diabetes is commonly believed to occur more often with men than with women. When, however, large numbers of cases are collected there seems to be some doubt as to the accuracy of this generalization. The following table from the Mortality Statistics, Bureau Census, 1909, p. 588, indicates the relation of the disease to sex and the frequency during various periods of life. It is most common after forty and is a rare

[7] Lion and Moreau: Arch. de Med. des Infants, 1909, xii, p. 21.
[8] Senator: Deutsch. med. Wochenschr., 1897, June 10.

disease before twenty, although no age is exempt. It has been noted in new-born infants.

Years	Male	Female	Years	Male	Female
Under 5	38	45	40–49	345	354
5– 9	51	65	50–59	592	703
10–14	68	107	60–69	760	950
15–19	113	71	70–79	456	527
20–29	205	161	80–89	118	108
30–39	232	187	90	9	3

In Germany much emphasis is placed upon the association of obesity with diabetes. That relation seems to me much less striking in America than in Germany. In hospital service here the diabetic who is or has been overweight is the exception and of the obese cases in my private practice nearly all have been Hebrews.

There is a form of alimentary glycosuria which I have encountered so frequently in association with gout that I have come to regard it as somewhat characteristic of that disease. I refer to that form of alimentary glycosuria which manifests itself in the urine voided after dinner while during the remainder of the day there is no sugar excreted. It will be found with these persons, usually men of robust physique who have had one or more attacks of gout, that if the urine voided during the six hours after dinner be saved separately from the rest of the twenty-four hour collection this will contain a small amount of sugar

while the remainder will not. This fact simply indicates an excessive consumption of starches (and sweets) at one meal and a lowered tolerance. Some of these cases ultimately become true diabetics. I have seen two cases of mild diabetes that I had studied some years previously as cases of gout and had then observed the alimentary glycosuria referred to.

A small percentage of the cases of diabetes may be traced to some immediate etiological factor. Thus there are instances where glycosuria has been first noted after acute infections, influenza, tonsillitis, and syphilis. A number of cases have dated from severe injuries. Ebstein analyzed the cases of "traumatic diabetes" and found that half of these had received injuries to the head. The relation of transitory sugar excretion to fracture of the skull is mentioned in the chapter on Pathology.

Emotional influences have been held accountable for many cases of diabetes since Willis commented that the disorder followed " sadness or long sorrow." Some examples of the coincidence between the onset and emotional disturbances are remarkable. A well-known case is that of an officer who acted as second for a friend who was killed in a duel.[9] During the ensuing two months the officer became much depressed and lost weight and it was discovered that he was suf-

[9] Seegen: Der Diabetes Mellitus, Leipzig, 1870, p. 64.

fering from diabetes. Dickinson [10] records a somewhat similar case of a mother who saw her child fall from a third-floor window. It was at first supposed that the child was mortally injured, but, although it survived, the mother was unable to eat or sleep for three weeks after the accident. Shortly after she developed excessive thirst and died of diabetes within ten months. There are many other cases scattered through the literature.

A boy four years old was brought to me with the history that the child had been in a runaway accident a month before. He was uninjured but badly frightened and the day following the accident began to drink large amounts of water. As this, with the excessive urination, continued, a physician was consulted and sugar detected in the urine. The child lived but four months from the time of the fright. Similar cases where the onset of the disease apparently dated from a fright or excessive anxiety have come to my attention. These have usually been in young individuals.

Occasionally pregnancy seems to be an etiological factor. In one case of my series there had been a pronounced glycosuria during two pregnancies which had entirely subsided after the birth of each child so that there was no sugar in the urine and no dietetic restriction was employed. During the third preg-

[10] Dickinson: Diabetes, London, 1875, p. 75.

nancy there was observed not only glycosuria but also a moderate increase of thirst and following the termination of this pregnancy the sugar excretion and the symptoms persisted. The woman became a typical diabetic. In another case the diabetes developed during the first pregnancy. Frank [11] concluded that a renal type of diabetes is so common during pregnancy as to be regarded as normal.

[11] Frank: *loc. cit.*

VIII

PATHOLOGY

THE researches of Claude Bernard formed the first secure basis for pathological studies. These investigations were directed in the first instance to the central nervous system and the liver. Indirectly much of our work at the present time may be traced to the initial impetus of this French physiologist. Although the most careful study of the brain and cord has failed to reveal constant lesions to which may be assigned etiological importance for diabetes, the work has not been fruitless. While the number of cases on record are very few wherein an injury or localized disease process in the brain or cord could be demonstrated as a cause for diabetes, yet the relation of these factors to glycosuria is well recognized.

Traumatism of the head and upper vertebræ is frequently followed by transitory glycosuria. Jodry [1] examined 145 cases; of these the injury was to the head in 50 per cent.; to the cord in 20 per cent.; while in 17 per cent. the location of the injury was not diagnosed. Of twenty cases of fracture of the skull admitted to New York Hospital I found sugar in the

[1] Jodry: Lehre Diabet, 1909.

urine within the first twenty-four hours in fourteen (70 per cent.). According to Lépine melituria manifests itself in the majority of these cases at some time during the first week after trauma. It is the consensus of opinion that a permanent diabetes dating from such injuries as these described is exceedingly rare, although a few cases are conceded. Besides injuries due to external violence hemorrhages in the brain or cord are occasionally accompanied by sugar excretion and may in hospital practice give rise to diagnostic embarrassment. Such was the case of a young man admitted to New York Hospital. He was in coma on admission and no history was obtainable from his friends. Sugar was found in the urine, which appeared to point to a diagnosis of diabetic coma. At autopsy a small hemorrhage was found in the medulla, probably due to a ruptured aneurism, since other aneurismal dilations were noticed in the same artery. It appears improbable, judging from the good state of this patient's nutrition, that he was a diabetic; and it is certain that the diagnosis was not properly grounded. The glycosuria was secondary to the injury of the nervous system.

Tumors of the central nervous system have been noted in association with persistent glycosuria in a number of instances. To Levrat and Pérrotton [2] the

[2] Levrat and Pèrrotton: Thesè, Paris, 1853.

earliest case of this nature is commonly accredited. A tumor of the choroid plexus was found in their case, and von Recklinghausen reported a similar observation. Softening, sclerosis, hemorrhage, and cysticerci in the neighborhood of the fourth ventricle have been observed in association with glycosuria.[3] Likewise lesions in the cervical or dorsal cord have been met with. Glycosuria is occasionally found along with meningitis, tabes, and multiple sclerosis.[4] It is difficult to estimate the significance of these changes in the central nervous system in their relation to a constant glycosuria. That such findings are exceptional is attested by the analyses of Seegen, who found in the autopsy protocols of the Allgemeine Krankenhaus that only nine per cent. of the cases of diabetes gave evidences of pathological alterations in the nervous system.[5] In many of these instances the lesions were doubtless secondary; moreover an analysis of four hundred and eighty-five cases of brain tumor by Bernhardt showed but five with glycosuria. Of these, two were tumors of the pituitary, one each of the medulla, cerebellum and hemisphere. And an elaborate summary of the nervous lesions found in association with diabetes made by Rosenberger rather tends

[3] Frerichs: Uber Diabetes Mellitus, 1893.
[4] Schultz and Knauer: Alleg. Zeitschr. f. Psychiatrie, 1909, 66, p. 759.
[5] Seegen: Der Diabetes Mellit., 1893.

to show that the connection is casual in most instances.[6] A striking fact which appears in all the reports is that a glycosuria is quite as apt to result from a lesion remote from the " diabetic centre " as from one near to it. The explanation offered that lesions are not irritative can be accepted only with considerable reserve.

The association with tumors in or near the hypophysis, however, suggests much more clearly a causal relation. The complication of acromegaly with diabetes has been given considerable attention and many observations are available. A frank glycosuria or lowering of the assimilation limit as evidenced by an alimentary sugar excretion has been observed in a large percentage of the cases. Of 176 cases collected by Borchardt[7] there was diabetes present in 63 and alimentary glucosuria in eight, viz., 40 per cent. showed weakness of the carbohydrate metabolism. Cushing and his pupils have shown that the pituitary gland is important in regulating sugar metabolism.[8] This function is more intimately related to the posterior lobe of the hypophysis, the removal of which in dogs increases markedly the tolerance for carbohydrates and the intravenous administration of extracts of this lobe causes glycosuria. From the evidence

[6] Rosenberger: Die Ursachen der Glycosuria, München, 1911, p. 287.
[7] Zeitschr. f. klin. Med., 1908, 66, p. 332.
[8] Cushing: The Pituitary Body and its Disorders, 1912, pp. 17, 261.

thus far obtainable it is to be inferred that glycosuria might be expected to result from tumors of the hypophyseal region where the posterior lobe or the stalk of the pituitary is involved, either directly or by pressure. On the other hand, processes resulting in diminished activity of this lobe are associated with increased tolerance for glucose. By no means are all cases of acromegaly accompanied by melituria;[9] whether there be as a rule diminished tolerance it is not possible to state,[10] since many reported cases of this disease have not been studied from this point of view. In one case of acromegaly which I was able to study over a long period of time there was no diminution in the tolerance, although at autopsy marked hyaline degeneration of many islands of Langerhans was noted. There was also hypertrophy of intact islands which, possibly, is the explanation for the absence of diabetes.

The early importance assigned to the liver as a storehouse for glycogen caused this organ to be studied with particular care in cases of diabetes mellitus. A case of cirrhosis of the liver and diabetes in an alcoholic subject interested Bernard because as the cirrhosis progressed there was a diminution of the sugar excretion to mere traces. Bernard interpreted these facts as indicative of excitation of

[9] Claude: Compt. Rend., 1911, 71, p. 75.
[10] Rotky: Zentralblatt f. Physiol. u. Path. d. Stoff., 1911, p. 173.

the glycogenolytic function by the disease process which later totally destroyed this function as marked by the disappearance of sugar from the urine, a view that has only an historical interest. The association of cirrhosis with diabetes is not, however, very common. Naunyn noted twenty-nine instances among two hundred and eighty-six cases of diabetes (ten per cent.), not a large proportion. That the diabetes is not dependent upon the cirrhosis is supported by Frerichs' observation of cases of cirrhosis with extreme degeneration changes without any evidence of diabetes during life. The frequency of association of degenerative changes in the liver and pancreas, however, has been remarked by many pathologists. From a detailed study of the lesions in the pancreas accompanying various types of cirrhosis Lafas arrived at the conclusion that the changes in both organs are a result of the same etiological factors, and that the pancreatic changes are not dependent upon those in the liver.[11] Hirschfeld appears to concur in this opinion and adds that the noxious agent, whatever it may be, is very seldom transported to the liver by way of the portal vein but when so conveyed the liver alone suffers. When, however, the agent is conveyed by the arterial circulation both pancreas and liver are affected. An illustration of this state of

[11] Lafas: Arch. gen. d. Med., 1900, III, 539.

affairs where both liver and pancreas are simultaneously damaged by a single agent is found in the condition described by von Recklinghausen as hæmochromatosis. In this disorder there is found along with degenerative processes in the cells of the gastro-intestinal tract, heart and kidneys, a general deposition of pigment throughout the tissues, cirrhosis of the liver (cirrhose pigmentaire), and chronic interstitial pancreatitis. Probably a more complete development of this disorder was described by Hanot and Chauffard[12] as Bronzed Diabetes; the pathological lesions are the same as in hæmochromatosis only that the pigmentation is more intense. Opie believes hæmochromatosis to be a clinical entity and that the diabetes becomes manifest in consequence of advanced pancreatic degeneration. The pancreatic lesion in this disease is of the interacinar type of chronic inflammation and implicates the islands of Langerhans, in consequence of which glycosuria ensues.

The opinion of Rössle that diabetes may be diagnosed at autopsy with more certainty from the hepatic changes than from the pancreas has not met with confirmation.[13] In addition to an increase in the weight of the liver which Saundby remarked, Rössle called attention specially to a fatty degeneration of

[12] Hanot and Chauffard: Rev. de med., 1882, II, p. 385.
[13] Rössle: Verhn. deutsch. path. Gesellsch., 1907.

Kupffer's stellar cells and certain refractile bands along the capillaries which are said to be characteristic.

The liver in diabetes is often large and fatty but consensus of opinion, however, is that there are no constant or characteristic changes in this disease.

PANCREAS

The association of pathological changes in the pancreas with glycosuria seems to have been first suggested by Cowley (1788). He recorded as the significant fact disclosed by an autopsy on one of his cases of diabetes an atrophy of the pancreas and many calculi within the ducts. Chopart made a similar observation at a later date, and Bright reported an instance of diabetes in association with tumor of the pancreas. It does not appear that anyone regarded affections of this gland as responsible for the glycosuria until Bouchardat did so in 1846.[14] It was, however, to a perversion in the digestive function of the pancreas that Bouchardat assigned the diabetes. A quarter of a century later Lancereaux definitely attributed to pancreatic disease a type of diabetes remarkable for its severity and named by him " diabète maigre." More complete knowledge has disclosed the inadequacy of this division. The pancreatic theory of diabetes was finally established by the experimental

[14] Traité du Diabète, 1875.

work of von Mering and Minkowski, and these experiments stimulated a renewed interest among pathologists in determining the nature and significance of the lesions noted at autopsies done on cases of diabetes. Since the earlier studies in this field were made for the most part without the aid of the microscope it is as one might expect, that the frequency and character of morbid states found in the pancreas varied considerably according to different students. Judging from the macroscopic appearance of the pancreas a chronic sclerosis was the condition most commonly observed and this was found in from nineteen to thirty-six per cent. of the cases of diabetes examined. With the aid of the microscope many conditions were disclosed which had hitherto escaped detection and the frequency with which lesions were observed rose considerably (Williamson, 79 per cent.). The nature and frequency of the various lesions is shown in the following table compiled by Hansemann,[15] of fifty-four cases which he studied in the Pathological Institute in Berlin:

Atrophy (granular)	36
Fibrous induration	3
Complicated case	1
Normal pancreas	8
Pancreas not noted	6
Total	54

[15] Zeitschr. f. klin. Med., 1894, 26, p. 191.

In his last communication on the subject Hansemann asserted that changes in the pancreas are demonstrable in every case of true diabetes provided the gland be examined before autodigestion takes place. What the various lesions are that interest pathologists to-day we must consider somewhat minutely.

Doubtless influenced by a suggestion of Laguesse that the islands of Langerhans may be related to the internal secretion of the pancreas, Schafer [16] advanced the hypothesis in 1895 that pathological alterations of these structures are responsible for diabetes. Some slight confirmatory evidence to the theory was afforded by studies of Ssobolew in 1900, but to Opie is due the chief credit for what we know of these changes. Opie observed sclerosis or hyaline degeneration of the islands as the most striking lesions. These lesions vary in degree; in some cases studied no islands were left intact. Hyaline change may or may not be accompanied by connective tissue proliferation about the islands. The frequency of these lesions as noted by various competent pathologists appears in the following statistics collected by Opie.[17]

Pancreatic Lesions:

Interacinar pancreatitis (fine sclerosis)	125	(43.4 %)
Interlobular pancreatitis (coarse sclerosis)	13	
Lipomatosis	18	

[16] Schafer: Lancet, 1895, II, p. 321.
[17] Diseases of Pancreas; 1910, p. 321.

Calculi	9	
Cyst	1	
Carcinoma	5	
Focal necrosis	2	
Atrophy	65	(22.5 %)
Lesions of the Islands of Langerhans with Normal Parenchyma:		
Hyaline degeneration	6	3.8 %
Sclerosis	2	
Adenoma-like hypertrophy	3	
No Lesions of Pancreas:		
Pancreas normal	34	13.5 %
Pancreas normal; number of islands of Langerhans diminished	5	
Total	288	

A more satisfactory estimate is perhaps adduced from the results of a single observer studying a large number of cases as the following table from Cecil indicates:

1. *Chronic Inflammation of the Pancreas:*	
Interacinar pancreatitis; sclerosis of islands of Langerhans	39
Interlobular pancreatitis; sclerosis of islands of Langerhans	4
Interacinar pancreatitis; hyaline degeneration of islands of Langerhans	19
Interacinar pancreatitis with lipomatosis; sclerosis of islands of Langerhans	2
Interacinar pancreatitis with lipomatosis; hyaline degeneration of islands of Langerhans	1
Interacinar pancreatitis with hæmochromatosis	2
2. *Parenchyma Normal:*	
Lesions of Islands of Langerhans.	
Sclerosis of islands	4
Hyaline degeneration	7
Infiltration of leucocytes about islands	1
3. *Pancreas Normal.*	11

Reducing, then, these figures to percentages, Cecil found 88 per cent. of his cases showed definite changes in the islands; these lesions were a hyaline degeneration in 30 per cent. and a sclerosis in 54 per cent. Sclerosis of the islands is usually associated with chronic interacinar pancreatitis. The pancreas was normal in 12 per cent. of the series. Of these cases classed as normal the gland was small in some instances and there appeared to be a diminution in the number of islands. It is a remarkable fact that of the eleven cases studied by Cecil where the pancreas is normal nine may be classed as young individuals; the oldest thirty-two; the youngest nine years of age, and in all the diabetes ran a rapid course.

As to the various lesions noted by pathologists the question arises is any one of them related as a causal agent to diabetes and if so which one? Chronic pancreatitis is not so uncommon as formerly thought and by no means always attended by glycosuria; neither does an extensive destruction of the parenchyma of the gland as a rule cause diabetes since with cancer of the pancreas diabetes is exceptional. Sauerbeck found carcinoma five times in his series of 288 cases of diabetes. Acute processes in the pancreas attended with necrosis may bring about extreme destruction of the gland parenchyma, yet Egdahl found glycosuria

with only six out of one hundred and five such cases.[18]

Since the appearance of sugar in the urine is not the usual sequence of all forms of chronic pancreatitis nor of those morbid processes which entail considerable loss of the gland substance, it must follow that if a lesion in the pancreas is responsible for glycosuria this lesion must be in some element of the gland that often escapes injury in the more general inflammations. A case which may be significant is reported by Scott[19] in which the islands of Langerhans were the only recognizable remains of the gland in a case of malignant disease of the pancreas. There was no sugar in the urine. Opie argues that extensive degenerative changes may affect the parenchyma and leave the islands of Langerhans intact. On the other hand, the islands are often subject to hyaline degeneration where in all respects the pancreas is practically normal and in such instances there is a history during life of diabetes. Interlobular pancreatitis does not usually implicate the islands until the process is quite advanced. With these cases diabetes is exceptional. In support of Opie's theory is the statement of Sauerbeck that he has been able to find no cases of severe lesions of the islands of Langerhans that were not accompanied by diabetes. The positive evidence of

[18] Bull. Johns Hopkins Hospital, 1906, xvii, p. 265.
[19] Scott: Jour. Path. and Bact., 1907, xi, p. 458.

Weichselbaum is based upon the microscopic examination of the pancreas of one hundred and eighty-three cases of diabetes; in all lesions were found in the islands of Langerhans. These lesions are of three types: hydropic degeneration (most common in young individuals), sclerotic and atrophic islands, and, finally, hyaline degeneration.[20]

The so-called insular hypothesis has been considered first because it is doubtless the dominant theory at the present time. The older acinar hypothesis has, however, able advocates. Hansemann [21] claimed in 1894 to distinguish in a "granular atrophy" the characteristic lesion of diabetes. Opie designates the same change as an interacinar fibrosis. Hansemann places special stress upon changes in the acini, and in his later papers [22] he has supported Herxheimer in contending that the islets are not independent structures but are constantly formed from acini and that these structures bear no relation to diabetes. This doctrine is also advocated by Karakascheff of Marchand's laboratory. Though not subscribing to the idea of

[20] In a case of acromegaly that I examined many of the islands of Langerhans showed a marked degree of hyaline degeneration. There were also to be found occasional islands that appeared normal and were hypertrophied. There was in this case no glucosuria. It is conceivable that the few intact islands by hypertrophy were adequate to the demands. Ohlmacher has mentioned a similar case.

[21] Zeit. f. klin. Med., 1894, 26, p. 191.

[22] Berlin. klin. Wochenschr., 1912, 49, p. 927.

transitions of acini into islets, Lomboroso has given his support to the theory that some disorder of the pancreas as a whole is accountable for diabetes.[23]

These in brief outline are the theories held by the pathologists at present. An impartial observer must be struck in reviewing the evidence presented with the large place held by the personal equation. It seems doubtful if agreement could be made as to the nature of a specific lesion and equally doubtful in many cases if diagnosis of diabetes could be established with facility by examination of the pancreas without knowledge of the clinical history. From the experimental side some evidence has been secured in support of the theory that the lesions of the islands of Langerhans are accountable for diabetes. By ligating the pancreatic ducts of a dog MacCallum [24] produced an extreme grade of degeneration so that after a year only a vestige of pancreas remained. This remnant of pancreas was composed practically entirely of islands. The atrophy of the gland was not accompanied by glycosuria, but when this remnant of pancreas was finally removed the dog developed at once an intense and persistent glycosuria. Other experimenters [25] have ligated the pancreatic ducts in

[23] Ergeb. der Physiol., 1910, 9, 1.
[24] MacCallum: Johns Hopkins Hospital Bull., 1909, 20, p. 255.
[25] Pratt: Arch. of Intern. Med., 1911, 7, pp. 665–679.

various animals with results that are not in entire accord. By some it is claimed with MacCallum that only islands remain in non-diabetic animals. Others find acini as well as islets. So the validity of the island doctrine cannot be held established by these experiments. That the pancreas undergoes marked atrophy after ligation of the ducts is admitted but the finding of islets only in this atrophied remnant does not overthrow Herxheimer's assertion that these islets simply present the last and most resistant state of acinar transformation. The experiments of Allen [26] are more to the point. He found in a large number of animals that after duct ligation the acinar tissue might be well preserved and yet diabetes develop. "The contrast between the two series (non-diabetic and diabetic) seems to be found in just one point; in the former series, preservation of the islets; in the latter, degeneration of the islets." While evidence at present is mostly favorable to the island hypothesis the question must be left open as demonstration is lacking.

Finally with regard to these cases of diabetes where no lesions are demonstrable in the pancreas, it is conceivable as Opie has suggested that simply a diminution in the number of islands (congenital) may give rise to diabetes. This seems possible. It is also

[26] Allen: Glycosuria, Boston, 1913, p. 980.

probable that we shall recognize in the future several types of diabetes, at present not differentiated, entirely independent of pancreatic disease; such as that exemplified in disease of the hypophysis.

In considering the anatomical findings in the heart and kidneys due regard has not usually been taken of the age of the patient. The pathological lesions that have been most often noted in those tissues are found almost exclusively in the older individuals.

The lesions of the heart in diabetes are changes in the myocardium. In cases with advanced sclerosis of the arteries it occasionally happens that the valve cusps may be involved in the process and thereby produce incompetence, but this is not of peculiar significance. Also fibrinous pericarditis or adherent pericardium is sometimes observed in cases of long standing, usually in association with sclerotic kidneys. Older writers make reference to an hypertrophy of the heart occurring along with renal hypertrophy. This is probably to be regarded as secondary to renal disease also. The degenerations of the myocardium are chiefly of the fatty type and are found in over three-quarters of the cases where any lesion is notable. Exceptionally there is brown atrophy. The glycogenic degeneration described by Frerichs is analogous to that observed in the kidney. In young patients and in children I have observed no change in the myocardium other than a

slight cloudy swelling of the cells in cases that have died in coma.

The kidneys in these young subjects have been quite normal except for a moderate degree of fatty change in the cells—a picture very common in all emaciating diseases. In the older subjects of diabetes a normal kidney is exceptional, at least in my experience. Seegen noted parenchymatous nephritis as the most common lesion in his series of cases at the Vienna Pathological Institute, contracted kidney forming less than one per cent. Since arteriosclerosis is so commonly an accompanying disorder with diabetes it is not remarkable that the kidneys are frequently diseased. The type of lesion is that form of diffuse nephritis which is commonly spoken of in America as the arteriosclerotic kidney. There is not, however, much reduction in the total renal substance and the glomerular tufts are more apt to present hyaline changes than complete fibrosis.

Frerichs and Ehrlich have described as characteristic of the kidney in diabetes a form of glycogenic degeneration. This observation lacks confirmation in recent literature though the lesion is familiar to pathologists since it is noted in the liver and some tumors.

There have been no studies made of the kidneys in "renal diabetes" that offer an explanation of this disorder.

BLOOD IN DIABETES MELLITUS

The water content of the blood in diabetes is subject to considerable variation. The normal percentage of water in blood is about 78, and in diabetes there appears a slight tendency toward concentration; with some cases of coma there has been noted as low as 73 per cent. of water and to this fact Rumpf [27] has assigned special significance in explaining the coma. This observation has not been substantiated by further investigation and the fact is explicable in the coma state by the loss through the lungs and urine of fluid which is not replenished by the usual ingest. That concentration of the blood is unusual is evidenced by the freezing point which is usually within normal limits. The variations have been studied by refraction methods with like results.[28] Unless there are complications to the diabetes the number of erythrocytes and leucocytes is normal. In advanced cases with marked loss in weight an anæmia of the secondary type may be noted, but it is often remarkable that the hæmoglobin is found but little diminished with very severe cases. The two most characteristic alterations of the blood in diabetes are the increase in its content

[27] Rumpf: Zeit. f. klin. Med., 1902, 45, p. 260.

[28] Refraktometrische Blutuntersuchung. Reiss. Ergeb. f. inn. Med. u. Kinderheilk., 1913, x, p. 595.

of sugar and of lipoids. An hyperglycæmia is found at some period with all diabetics. The amount of glucose recoverable from normal blood depends to some extent upon the method of analysis employed and varies between .06 and .12 per cent. Under conditions of disease these amounts may be increased several fold. With severe diabetes it is not unusual to find values of 0.3 per cent. or over; and Weiland noted .79 per cent. and .95 per cent. in coma cases. Exceptionally very high figures for blood sugar are also observed in uræmic coma; in one of my cases .51 per cent., though there had been no sugar in the urine during the period prior to coma nor was there anything in the history that suggested diabetes. A moderate increase in the blood sugar without glycosuria is observed in fevers and with exophthalmic goitre. The degree of hyperglycæmia with diabetic patients depends on several factors. First among these is the severity of the disease. In young patients where the course of the malady is rapid the blood sugar is much higher than with elderly patients in whom the disease may occasion few or no symptoms. It may often be observed again, that in the earlier stages there is but slight hyperglycæmia but later as the tolerance diminishes the increase in blood sugar is twice or thrice normal. A man of 51 years sought advice in June, 1912, for what appeared to be a mild type of diabetes. It

was found by tests that he could utilize 80 grammes of starch. His blood sugar, before treatment was begun, was .17 per cent. During the next nine months the urine remained free of sugar with a carbohydrate tolerance of 70 to 80 grammes. In 1913 following a period of hard mental work, sugar appeared in the urine in considerable amounts and investigation revealed that he could not utilize more than ten grammes of ingested starch. The blood sugar had increased to .29 per cent.

When treatment is met with success and the urine can be kept glucose-free for a period there is a gradual fall in the glucose of the blood to nearly or quite normal amounts. This response in the blood is not immediate however. With many cases it is found that notwithstanding the fact that there has been no sugar excretion for a couple of weeks or more, yet the values for blood sugar are .05 to .08 per cent. above normal. Just what explanation is to be given for the absence of glycosuria under these circumstances is not entirely clear. It has been assumed that a lessened permeability of the kidneys exists and with many cases there may be ground for suspecting nephritis. But it might appear that an adequate explanation would also clarify the absence of glycosuria with non-diabetic hyperglycæmia. The reasons may lie in the state of the blood sugar, as some, notably Lépine, believe.

The doctrine of a colloidal suspension of blood sugar has been discussed in another chapter.

A much more variable condition than the hyperglycæmia is a lipæmia. Normally the blood content in lipoid substances is about one per cent. An increase beyond the normal bounds is found not only in some cases of diabetes but also in severe anæmias, eclampsia, cholæmia, and occasionally in some other diseases. The highest percentages for blood fats have been observed in severe cases of acidosis; indeed, it appears to be intimately related to this condition, since in cases under close observation the lipæmia has disappeared with improvement and reappeared with exacerbations of the acid intoxication. Lipæmia is, however, by no means an invariable manifestation in severe acidosis, nor even in coma. When evident it is most pronounced in coma. Stadelmann found 15 per cent. of lipoid substances in one case; it is very exceptional though to find more than 4 or 5 per cent.[29] This increase is only in part due to neutral fat (triglycerides) since both cholesterin and lecithin are above normal, and the former may at times constitute 30 or more per cent. of the total lipoid of blood. The significance of this enormous increase in the fatty substances is not known. That it is not a consequence of

[29] Fischer: Ueber Lipamie u. Cholesteramie. Virchow's Arch., 1903, 172, p. 30.

the fat-containing diet has been shown,[30] and it seems equally doubtful if the cholesterin is to be regarded as a product of broken-down cellular tissue—a theory first advanced by Flint and recently revived. The importance of lecithin and like substances in serology has awakened a renewed interest in the whole subject [31] and it may be expected that the problem of lipæmia will be solved in the not remote future.

[30] Klemperer and Umber: Zeit. f. klin. Med., 1908, 65, p. 340.
[31] Burger and Beumer: Berlin. klin. Wochenschr., 1913, 50, p. 112.

IX

SYMPTOMATOLOGY

THE classic symptoms of diabetes, thirst, wasting, and increased urine volume, are mentioned in the oldest literature of the disease. These symptoms are not always present in a marked degree. Many diabetics who have passed the meridian of life do not lose weight and the urine excretion is hardly above normal. This difference, in connection with others to be mentioned, led clinicians to differentiate between the severest forms of the disorder and those where the course is less rapid. Formerly these types were designated as acute and chronic, now more generally by the descriptive terms severe and mild.

The mildest types of diabetes can undoubtedly exist for some period without producing symptoms. Several men have consulted me who first became aware of their condition on being rejected by insurance companies. These cases probably represent a very early period in the disease. They are usually in the fifth or sixth decade of life although one case was under thirty. Absence of symptoms is unusual; but with hospital patients the indications of disease are

frequently not observed. Here carbuncles, boils, pruritus, or gangrene of a toe is often the occasion for coming to the clinic. With more sensitive and introspective persons an increase in frequency of urination is sufficient annoyance to require investigation. Some cases are detected by the ophthalmologists in association with cataract. These examples serve only to show the bland form that the disease may at times assume and the variety of symptoms connected with it.

As a rule there is not only distressing thirst and polyuria but the history of some loss in weight. In severe forms, especially in children, the loss of flesh is rapid in the extreme, rivalling in this respect the febrile diseases. With these cases the amount of urine is sometimes enormous, ten or even fifteen litres per day. The rapid wasting is readily explained by the loss in sugar through the urine. One of my cases, a young woman, voided daily an average of eight litres of urine containing from 500 to 600 grammes of sugar; a loss to the body of from 2000 to 2500 calories. This loss of sugar accounts not only for the emaciation but also for the weakness and the voracious appetite. It is, under such conditions, almost impossible to consume sufficient food to keep pace with the disease unless the diet be arranged to meet special demands.

Many diabetics have a type of facies that is characteristic; so much so that some students of the dis-

ease have believed a diagnosis possible on inspection. The characteristic element is the patient's color. This may be so brilliant as to suggest blooming health. Closer attention, however, reveals a difference from normal in that the ruddy tint is deeper than normal pink, approaching the red of sunburn, and spreads from high on the cheek, fading only on the neck. This diabetic complexion, if it may be so styled, is usually noted with young patients and then there are often evident the lines about the mouth which one associates with rapid loss of weight. Aside from the polydipsia, polyuria, and wasting, there are few symptoms usually noted in the early stage of the disease; the majority may quite correctly be regarded as complications or sequelæ. An abnormal appetite accompanies the severe types of the disease and is a direct consequence of the enormous sugar loss through the urine. Many patients complain of an unpleasant taste in the mouth. Dr. Camplin, a friend of Bright, himself a diabetic, described this taste as "sweetish and cloying." It has been repeatedly likened to the taste imparted by a coin in the mouth. Not infrequently there are cramps in the legs, particularly in the calves; coming on at any time, but especially at night. This symptom has been attributed to a mild neuritis.

Ordinarily digestive symptoms are lacking. One meets occasionally with various types of dyspeptic dis-

turbances but these are not characteristic. The tongue is sometimes coated; more frequently red and dryish. The teeth are very prone to suffer rapid decay in diabetes owing perhaps to abstraction of the lime in those cases complicated by acidosis. With adults there is a decided tendency to contract pyorrhœa alveolaris, which is observed generally with all diabetics in hospital. Constipation is common, due to loss of water from the intestine. With children this may be a most distressing and difficult symptom to combat.

A long list of skin disorders have been more or less correctly attributed to diabetes. The fact that diabetics usually do not sweat or do not have a normal amount of perspiration may be the reason for the dryness of the skin one commonly notes. There are observations to the effect that the sweat and tears of diabetic patients contain sugar; but this requires confirmation. Some authors have held that psoriasis is peculiarly common with diabetics, but Naunyn thinks the association accidental. In some of his cases the skin lesion antedated the glycosuria. Among other affections of the skin one may encounter are xanthoma, chronic urticaria, and impetigo. The frequency of acne is in some measure due to the drugs commonly employed with diabetes. Among the older patients eczema is almost universal, it may be very extensive and occasion great distress. A peculiar itch-

ing of the skin unassociated with any visible lesion is sometimes observed.

Pruritus vulvæ is often the first symptom of diabetes in women who have passed the menopause. The symptoms result from irritating urine and quickly subsides if the sugar excretion is controlled.

Of the infections of the skin besides acne, boils and carbuncles are common. In hospital practice these are often the first symptoms which prompt the patient to seek medical aid. With carbuncle in an adult patient the urine should always be tested for sugar. Less met with is perforating ulcer of the foot, *malum perforans pedis.* It is encountered usually in old subjects. Apparently it may be a diagnostic pitfall since two of my series had been pronounced tabetic on account of the ulcer and absence of knee jerks.

Diabetics are peculiarly prone to nervous disturbances. Besides the cramp-like pains in the legs, already referred to, a frank neuritis is often seen. This may involve any nerve trunk but is more usual in those of the lower extremity. The neuritis may be of either the sensory or motor type. A woman of sixty suffered from neuritis of both sensory and motor type in the left leg. In the course of several months she became free of pain but the tibialis anticus muscle was left paralyzed. A year later the same sequence of events occurred in the other leg. Neuritis of the

sensory nerves may occasion the severest pain and persist for months. In these disturbances improvement in the diabetic symptoms is not always followed by an amelioration of the nervous symptoms. Absence of the patellar reflex is also to be regarded as a neuritis. The prognostic significance attached by some members of the French school to a negative Westphal sign is scarcely warranted by facts. This sign may fail early in mild cases of diabetes and is usually absent in those of long duration.

An interesting symptom is intermittent claudication. It is scarcely permissible to attribute this to a neuritis; it is possibly secondary to anæmia of nerve centres in consequence of advanced arteriosclerosis.

Diabetic patients of all ages may suffer from herpes zoster; but I have met with it most often in young adults and children. One child, a girl of seven years, experienced two attacks in a period of six months. The pain following the disappearance of the vesicles is fortunately frequently absent with children.

It is not clear whether impotence is to be regarded as of nervous origin or is an effect of the profound metabolic disturbances. This symptom is occasionally among the earliest indications of the disease.

Of the symptoms related to the eye, cataract is by far the most common. Diabetic retinitis occurs of two types; with exudate and with hemorrhage—centralis

punctata, and hæmorrhagica. A peculiar sluggishness of pupillary reaction to light has been described by Grube but it is of rare occurrence.

The vulnerability of the diabetic patient to infection is proverbial. Whether this fact be due to the sugar content of the tissues, as some believe, or whether the fault be of a deeper nature had best be left an open question. Slight wounds, or a bruise, may become infected and result in a lesion dangerous to life. A small blister on the foot from the friction of a new boot causes first an ulcer and then osteomyelitis. Some of the cases of gangrene of the toes have this origin. Not so many are neurogenic as is supposed. A small percentage are probably dependent on extreme narrowing of the sclerosed arteries but the vast majority are infective.

Likewise the vulnerability of the mucous membranes is notable. Cystitis is common, also chronic bronchitis and pulmonary tuberculosis. Colds are contracted with ease; pneumonia is usually fatal. Pulmonary gangrene sometimes develops with an acute onset and signs not to be differentiated in the beginning from pneumonic consolidation.

Menstruation usually ceases with severe cases of diabetes. Where the disease is less profound there is irregularity and scantiness of flow. Conception is most frequently followed by early abortion; with a

minority, pregnancy terminates with late abortion; while a small percentage give birth to living children. Pregnancy is correctly regarded as a great hazard for a diabetic woman, since the disease is sometimes rapidly progressive during this period or terminates in death shortly after delivery. If a living child is born the chances of its survival are much diminished. Offergeld [1] noted that when pregnancy is complicated by diabetes thirty per cent. of his cases died in coma before the completion of the pregnancy and of those that survived pregnancy twenty-four per cent. died within thirty months. Hydramnios occurred in ten of his sixty-three cases. Of twenty-seven children born alive but fifteen lived longer than two years. It is now generally believed that the danger of pregnancy in diabetes is comparable to that in patients suffering from tuberculosis and severe valvular disease. Rarely it does happen that the diabetes is less severe or even vanishes during the period of pregnancy. A woman whom I saw in consultation was in better general health during two pregnancies than in the interval and the glycosuria much less. She is still alive three years after the last pregnancy. It was impossible to demonstrate with this patient that the diabetes was of the renal type.

The urine with diabetes presents other interesting

[1] Arch. f. Gynaekolog., 1908, Aug. 15, p. 630.

features than the sugar. The excretion of the latter may be almost incredibly large, up to over a kilo per day. Exceptionally the sugar is not all glucose; levulose has been found in a few cases as well as dextrose. The urinary volume is usually above normal and tends to be roughly in proportion to the amount of sugar excreted. With severe cases a daily output of eight or ten litres is not uncommon and a volume of even fifteen litres per day has been observed. Occasionally a considerable diuresis is found although the sugar excretion may be relatively small. There is in this respect some suggestion of a diabetes insipidus and cases of this latter disease complicating melituria are well known. The percentage of sugar in the urine may be small, less than one, yet the total glucose output for each day may be 25 to 50 grammes. This serves to illustrate the fallacy one invites if the *percentage* quantity of sugar is taken as a guide without respect to the total urine volume for the day. Fortunately the custom is almost abandoned in this country and is not recognized at all in Europe. The sugar excretion should ever be estimated as grammes for the twenty-four hours. In no other way can anything like an adequate knowledge of the patient's conditions be secured.

Nitrogen elimination depends on the protein intake; as this latter is usually large the urinary nitro-

gen is above normal. While with the average man the total nitrogen in the urine is between fifteen and thirty grammes, the diabetic consumes so much protein that the nitrogen excretion may be forty or even fifty grammes per day. With a few severe cases where the physician had ordered meat and eggs as the chief ingredients of the diet I have noted nitrogen excretions of some fifty grammes. In cases where the protein ingest is restricted and the nitrogen elimination exceeds the amount taken in, the difference is due to the catabolism of body protein, as can be readily demonstrated by the loss in body weight.

The question of uric acid formation and its possible destruction in the normal human body is not as yet clearly understood. The quantity formed depends certainly on two, probably on three factors; the most important of which is the nuclein ingested in the food. Since animal foods are relatively rich in nucleins, derived from the nuclei of cells, it follows that the uric acid excreted is in large measure proportionate to the amount of this kind of food eaten. Diabetics as a class eat more meat than normal men and the uric acid excreted is consequently above the average normal excretion. It is not, however, out of proportion to the total nitrogen of the urine. These are factors which are so much influenced by the amount and kind of diet that no generalization without respect

to it is possible. With any diet of definite composition the proportion that each nitrogen fraction—urea, ammonia, etc.—bears to the total nitrogen fluctuates within narrow limits but this is true only so long as the diet remains unchanged in amount and composition. With normal man on a mixed diet the nitrogen excreted as urea fluctuates between 80 and 90 per cent. of the total nitrogen. In diabetes so long as there is no acidosis the normal proportions are retained; if the total nitrogen be thirty grammes about ninety per cent. of this will be found as the urea nitrogen, the remaining ten per cent. is composed of the nitrogen in ammonia, creatinin, uric acid, and amino-acids. When, however, free acids are elaborated as products of metabolism these acids are in part neutralized in compounds with ammonia and are excreted in the urine as salts. Ammonia so combined with acids within the body does not of course arrive at its normal end-product, urea. This is shown quite clearly in the urine of acidosis cases in that the urea excretion falls while the ammonia nitrogen increases. Under the administration of alkalies to the patient the reverse process ensues and in mild cases of acidosis a normal nitrogen partition may be effected. The normal nitrogen fraction excreted as ammonia is something less than one gramme per day and under any condition giving rise

to acidosis this figure rises considerably and is a valuable index to the degree of the intoxication. In diabetes one frequently finds the ammonia nitrogen amounts to two grammes per day when there are no evident symptoms of acidosis. When, however, this figure rises to three grammes we have to do with a condition dangerous to the patient. It is then an indication for alkaline therapy and the other means of combating acid intoxications. An excretion of four grammes of ammonia nitrogen daily has never in my experience persisted for more than a few days without the development of coma. During the period of coma the ammonia excretion may be enormous, especially in cases where there has been no administration of alkalies. Stadelmann found twelve grammes of ammonia in a case of diabetic coma. In a similar case admitted to hospital in coma I found 3.4 grammes of ammonia nitrogen per 100 c.c. of urine in a catheterized specimen; a figure that would indicate 10 grammes per day on a conservative estimate (3000 c.c.). When severe acidosis prevails the ammonia nitrogen forms a high per cent. of the total; as coma impends, forty or even fifty per cent. of the total nitrogen may appear in the urine as ammonia. Under these conditions there is a corresponding fall in the nitrogen excreted in the form of urea.

Until recently there has been no trustworthy method for estimations of the amino-acid content of urine. Several methods are now available and in a short while our knowledge will be more complete in this respect. Employing the naphthalin method, Abderhalden found appreciable increases over normal of the amino-acids in two diabetic urines. One of these cases suffered from a terminal pneumonia and the other was in coma. In a third case no increase was detected.[2] An increase was also noted in the urines of deprancreatized dogs by Labbé. More recently Löffler[3] has examined four cases employing the Van Slyke method. An increased amino-acid output was observed in all and this was most marked in the severest cases of diabetes. Whereas a normal output is found to be about .1 gramme per day in severe diabetes the figure rises to 0.26 or even 0.7 grammes. The significance of this increase is not clear from the data at hand. It suggests some profound disturbance of cellular metabolism. An hypothesis has been advanced by Hugounenq that the terminal coma is less a consequence of the abnormal ketone formation than of the products of protein disintegration. Such a view lacks adequate basis at present.

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[2] Zeit. f. physiol. Chem., 1905, 44, p. 17.
[3] Löffler: Zeit. f. klin. Med., 1913, 78, p. 485.

KETONE BODIES

The presence in the urine of acetone and β-hydroxybutyric acid is by no means characteristic of diabetes. Small amounts of acetone are normally found, and in fevers the increase is considerable. It has been repeatedly observed that the von Laube treatment of gastric ulcer gives rise to a mild acidosis notable in a strongly marked Gerhardt's reaction in the urine and detectable amounts of acetone and hydroxybutyric acid. Several years ago when fasting was in vogue as a cure for all ills a normal man abstained from all food for five days. The urine was collected for me during the fourth day of the fast. The analysis is:

Amount.	Total N.	NH_3–N.	Acetone and diacetic acid.	β-oxybutyric acid.
c.c.	gr.	gr.	gr.	gr.
1410	11.42	1.09 (9.6%)	0.475	0.819

The grade of acidosis represented here is comparable to that found in mild cases of acidosis with diabetes and was induced in this case purely by abstinence from food. Ketonuria of no greater severity than this occurs in many conditions and is seldom, if ever, accompanied by symptoms attributable to the acidosis. Acetone and diacetic acid in small amounts appear in the majority of diabetic urines at some period during

the course of the disease. With mild cases this is induced by changes in diet and is temporary; in other instances the ketone bodies vanish along with the disappearance of the sugar, while in the most severe diabetes, it is noted early that in spite of all means to prevent it there is a considerable and persistent excretion of these acids. Very large amounts may be found constantly for weeks and months before the onset of coma. In the case of a girl of nineteen I found constantly between five and six grammes of β-hydroxybutyric acid during the fourth month before coma. These figures gradually rose as the end approached. The following table gives a synopsis of some of the analyses during the latter months:

Date.	Urine.	Sugar.	Acetone diacetic.	β-oxybutyric.
	c.c.	gr.	gr.	gr.
Nov. 20, 1908.....	7600	481	5.04	14.40
Dec. 1, 1908.....	7680	530	6.87	22.45
Feb. 5, 1909.....	8100	596	10.11	70.08

Death came in coma Feb. 10.

In exceptional cases the β-oxybutyric acid excretion may be as much as 150 grammes per day during coma.[4] Of the total ketone bodies in the less severe degrees of acidosis the larger part is found as

[4] Magnus-Levy: Die Oxybuttersaure u. ihre Beziehungen zum Coma diabeticum, Leipzig, 1899.

acetone and diacetic acid. As the acidosis progresses and gradually becomes more and more pronounced there is an ever-increasing proportion of oxybutyric acid, up to 60 or 80 per cent. of the total ketone bodies, as Neubauer [5] has shown.

COMA

The widest variation is perceptible among diabetic patients in their resistance to acidosis. Naunyn remarked that some patients appear perfectly comfortable for years with a diurnal excretion of twenty or thirty grammes of oxybutyric acid. On the other hand, it is occasionally noted that symptoms commonly attributed to acid intoxication become evident when the total ketone bodies excreted are but ten or fifteen grammes per day although the alkaline dosage may be sufficiently large to secure proper elimination. For of course it is to be recollected that it is the retained acids that work the harm; and one knows that the excretion of these can be increased considerably if sufficient alkali be administered.

It is apparent from what has been said that there are to be found in the urine sufficient data to warn us of dangerous degrees of acidosis. And if careful and frequent urine examinations be made coma comes in a case as no unforeseen event. Only under the condi-

[5] Verhandl. d. deutsch. Congr. inn. Med., 1910, 27, p. 566.

tions where it is anticipated may one feel that all that is possible has been done to prevent it. Diabetic coma does not often develop suddenly but is usually preceded by several days, at least, of fairly characteristic symptoms. The patient complains of cramps in the legs and abdomen and there is intolerable lassitude. The appetite becomes capricious and slight nausea is common. Along with these symptoms there is usually some headache, which is attributed to obstinate constipation. A slight œdema of the ankles is often detectable. In the urine one may find a fall in the sugar output with high values for ammonia and ketone bodies. If vigorous treatment be employed during this stage some of the cases can be carried over a dangerous period and may live months longer. With many all means at our command are of no avail. The lassitude is followed by drowsiness which deepens gradually into profound coma from which the patient cannot be roused. After the prodromal state is well marked coma may develop very quickly. In one case, a young woman, there had been disinclination for exercise, mental torpor, cramps and slight gastric disturbances for three days. The urine had shown over three grammes of ammonia nitrogen for two weeks and 50 grammes of soda bicarbonate and citrate had been given, which was later increased to 70 grammes daily. On the fourth day the patient drove for an

hour in the park and on her return to the house said she felt much better. She rested for an hour before luncheon but felt no appetite and decided to go to sleep. At three o'clock she seemed stuporous and the family, having been warned, appreciated the significance of this symptom and summoned their physician. In the evening the patient was in profound coma which terminated in death on the next morning. Naunyn and others have reported cases where the death occurred within twelve hours after the first symptoms. One is apt to forget that diabetes may be a cause of sudden death; these cases, however, are rare. Although death in coma as a sequel of diabetes had been referred to by Marsh,[6] coma diabeticum was described first by Kussmaul[7] and to the clinical picture as he portrayed it little if anything has been added. The striking feature when one first sees the patient is the type of respiration. The respiratory movements are long and deep, involving all the muscles and suggest in the inspiratory phase the "long breath that precedes a yawn." The expiration appears more complete than normal, even forced. With this there may be increase in the respiratory rate which, however, is usually from sixteen to twenty per minute. The German term *"Grosse Atmung"* is ex-

[6] Marsh: Dublin Quart. Rev., 1854, 13.
[7] Kussmaul: Deutsch. Archiv f. klin. Med., 1874, xiv.

actly descriptive. As the period of coma lengthens there is commonly noted an increase in the respiratory rate which may reach to 40 per minute and there is then no evident pause between inspiration and expiration. The peculiarities of this type of dyspnœa disappear as death approaches. In no other disorder, save a few cases of uræmia, have I seen exactly the same type of respiration which characterizes Kussmaul's air hunger.

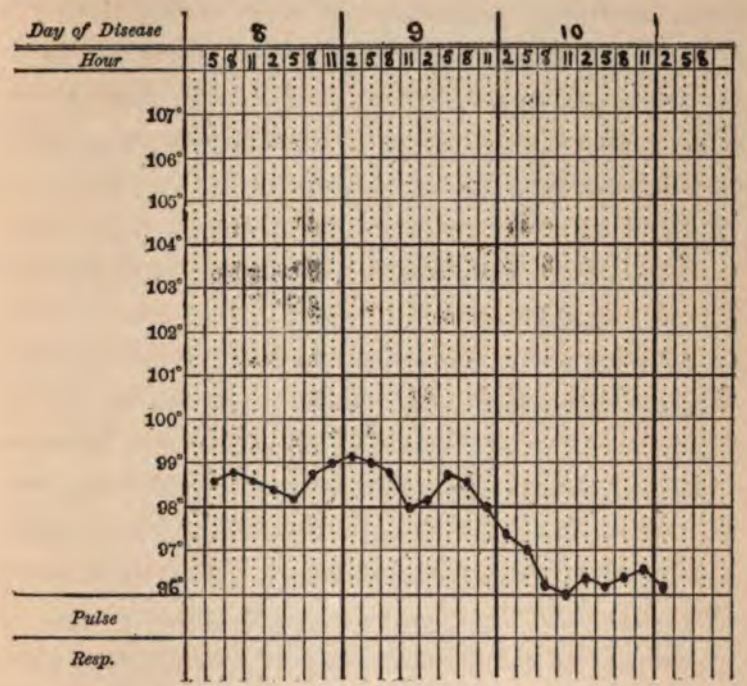
In one case in my series there was no suggestion of the Kussmaul air hunger. This patient gradually lapsed into coma and died after fifteen hours. The respirations were rapid and shallow throughout the coma period. Autopsy failed to disclose any complication to explain the atypical symptoms. Naunyn cites two cases as atypical in similar respects and there are eight others in the literature.[8] Also Cheyne-Stokes respiration may alternate with typical coma dyspnœa.

As to the mental state, it is dependent upon the duration of coma. At first the patient can be roused and is mentally clear; later, however, no response can be elicited. Delirium should excite suspicion as to the diagnosis.

The facies are flushed, often with a cyanotic tinge, and one may be deceived in the appearance of fever.

[8] Blum: Ergebnisse d. inn. Med. u. Kinderheilk., 1913, xi, p. 445.

The temperature rarely rises above 100° F. at the onset of coma and gradually falls until death; it is often subnormal and has been recorded as low as 90° F.



Several observations relating to the eyes are of diagnostic moment. The pupils are sometimes dilated, less often slightly contracted, and the light reflex is retained until late. Krause called attention to a peculiar softening of the eyeball which Schütz has shown to be due to a diminution of intraocular pressure.

This seems to be a very constant phenomenon which I have noted in all cases. On the other hand, I have never observed Loewi's mydriasis after applications of adrenalin. The vessels of the fundus may assume a peculiar whitish appearance in cases where there is a high degree of lipæmia. This, however, is variable.

Some acceleration of the pulse is the rule, but a rate above 120 per minute is exceptional. The pulse is very soft, and the blood-pressure falls as the coma period advances.

In many cases a slight œdema can be made out over the ankles.

This typical coma is observed in the great majority of instances. In a small percentage the picture is different in some essential respects. It is an open question with these atypical cases if we have really to do with coma diabeticum but as yet no differentiation can be made founded on causation. The chief variations relate to the type of respiration. In some of these cases the ketone bodies excreted in the urine have been relatively of low amounts. In others the cardiac weakness dominates the picture. The pulse is rapid, 140 to 160, and the heart sounds barely audible. In one of Frerich's cases there was no peculiarity of respiration but notable cardiac weakness; and von Noorden's case died before deep coma prevailed, apparently from cardiac failure.

A few cases are reported in the literature where coma has been ushered in by convulsions.[9] This is an exceedingly rare complication and in any event uræmia must be regarded as a possible explanation. Naunyn in his enormous experience has not encountered such a case. Janowski suggests that convulsions with diabetic coma are peculiarly common among the Poles.

Coma may develop with scarcely any warning during convalescence from infectious diseases. With two cases of pneumonia and one of erysipelas I have observed this termination. A man of forty-two had been under medical supervision for four years on account of a mild diabetes. In March, 1908, he contracted pneumonia. The infection did not appear to be a severe one but considerable apprehension was felt for him because of the diabetes. Defervescence by crisis occurred on the sixth day of the disease and on the seventh and eighth days the patient's condition was excellent. The urine besides sugar contained a trace of albumin and many casts. There was no Gerhardt's reaction but a strong acetone reaction. On the ninth day some nausea was experienced during the forenoon and the patient complained of breathlessness. Careful physical examination indicated a resolving pneumonia, nothing else. The afternoon of the same

[9] Losson: Zeit. f. klin. Med., 1908, p. 56.

day when I first saw the patient there was quite typical air hunger; sopor was marked but the patient could be roused to answer questions. There was nothing in the physical examination of significance. The temperature was 98.2° F., the pulse 90 per minute. A small specimen of urine was examined and found to be very acid: specific gravity 1032; sugar 1.3 per cent.; albumin, heavy trace; ammonia N, 0.32 gramme per cent.; total N, 1.9 grammes per cent.; diacetic and β-oxybutyric acids present. The patient was given soda bicarbonate by mouth and by enemata and 30 grammes of sodium carbonate intravenously, without, however, improving his condition. Death occurred on the afternoon of the tenth day of his sickness, following deep coma.

In the other case of pneumonia a similar sequence of events occurred.

With reference to the case of erysipelas the facts may be briefly summarized. This patient, a man of fifty, had been in New York Hospital for two weeks under treatment for a moderately severe diabetes. When he developed facial erysipelas it was expected he would quickly succumb. He was transferred to the isolation ward and to the astonishment of all concerned with him after ten days' sickness he began to improve rapidly. The sole untoward symptom was a marked ketonuria which he had had since admission. After

three days of normal temperature and marked gain in his general condition, air hunger developed. Coma followed rapidly and the patient died in twelve hours after its onset.

When the patient has been under observation and the signs of acidosis recognized the diagnosis of diabetic coma offers no difficulty. When, however, a comatose patient is brought to the hospital with no history and sugar is found in the urine considerable confusion may arise in differentiating coma diabeticum from some other conditions. It is to be remembered that uræmia, apoplexy, and meningitis are frequently terminal events in diabetes. Moreover, any disease giving rise to coma may occur as a complication in diabetes. The condition most commonly mistaken for diabetic coma is uræmia. With diabetic individuals over fifty years of age uræmia is often the cause of death. The fact has been frequently alluded to that a glycosuria of long standing may diminish or become intermittent and with such cases there is very often a marked increase in blood-pressure and retinal hemorrhages. The type of respiration usually found with uræmia has in it nothing suggesting Kussmaul's air hunger; neither does the urine give evidence of marked acidosis. When mistakes in diagnosis occur they are due to the fact that sugar in the urine is regarded as pathognomonic and all other evidence dis-

regarded. Sugar may occur in the urine temporarily in a long series of morbid states; marked ketonuria with high ammonia values very seldom. The following case is one of three wherein uræmic coma was not recognized.

A woman sixty-two years of age had been under treatment since 1899 for a mild diabetes. Sugar disappeared from the urine so long as she employed the diet her physician advised. In 1904 she found that her urine reports showed no sugar although she was not restricting her diet except in avoiding sugar. In 1905 she suffered from neuritis in the left arm and her blood-pressure was then 190 mm. mercury. During the spring of 1910 there were severe headaches and considerable loss in weight. The urine was examined at irregular intervals and was usually free of sugar, although small amounts, less than one per cent., were noted on a couple of examinations. In December, 1911, following several days of extremely severe headaches associated with nausea and slight vomiting, the patient became stuporous and finally comatose. The examination of urine showed a trace of albumin and sugar present (estimation not done), a moderate number of hyaline and granular casts, and a specific gravity 1023. The diagnosis of diabetic coma was made and advice sought. On examination the respiratory move-

ments were nearly normal. There was notable cardiac hypertrophy, a blood-pressure of 264 mm. mercury, albuminuric retinitis, intra-ocular pressure not reduced. The urine was not highly acid and contained a trace of acetone, but no diacetic nor oxybutyric acids. The patient recovered from this attack of uræmia and lived eight months. Death was due to typical uræmic coma. The respiratory movements in uræmia are very exceptionally of the Kussmaul type; the coma not so deep and slight delirium or disorientation is at least common. Moreover there is commonly slight fever and a leucocytosis. The ketonuria when present is of trifling grades resulting from restricted food ingest, and the urinary ammonia is never very high. With uræmia the urine is also quickly made alkaline by the administration of alkalies, a condition which is very difficult to bring about with diabetic coma. When it is possible to do so an estimation of the sugar and non-protein nitrogen in the blood may determine the diagnosis.

The glycosuria occasioned by fracture of the skull, hemorrhage in the medulla or pons, will never lead to error in diagnosis if proper examination of the patient be made. On the contrary, sugar in the urine is at times a useful aid in correctly interpreting the other signs.

COMA THEORIES

There remain for consideration the theories which have been advanced to explain the train of symptoms we recognize as diabetic coma. The older conception advocated by Naunyn and based upon the experimental work of Stadelmann is that of an acidosis. By this it is to be understood that some acid induces symptoms which are analogous to the artificial coma that may arise in animals if large amounts of acids be administered. This conception stands in contrast to the second theory that views coma as the effect of a specific toxin which in this case happens to be of acid properties. Now what are the criteria as we understand them of acidosis? If acids are produced in large amounts in the tissues four effects are noted: (1) A highly acid urine not readily made neutral or alkaline by administering alkalies; (2) a marked increase in the ammonia of the urine; (3) decreased carbon dioxide content of the blood and of the alveolar air; (4) increase in hydrogen ion concentration of the blood; *i.e.*, the blood is less "alkaline" than normally. Some or all of these criteria for the establishment of a condition of acidosis are found in many morbid states, as for example, in the removal of carbohydrates from the diet, starvation, fevers, and disturbances in circulation.[10] In these conditions symptoms do not attend

[10] Palmer and Henderson: Arch. Int. Med., 1913, 12, p. 153.

the mild degree of acidosis observed. In diabetes of the severest types and in coma there is always observed a marked increase in the ammonia of the urine and usually a decrease in the carbon dioxide content of the blood and alveolar air.[11] The urine in coma is so highly acid that an amphoteric reaction is effected only after the ingestion of large amounts (100–200 grammes) of bicarbonate of soda. In some cases at least[12] there has been found by electrochemical methods an increase of hydrogen ions in the blood, and by the less accurate titration methods an alkaline decrease. What then are the objections to the theory of acidosis since the criteria are apparently fulfilled in some of the cases of diabetic coma? It is usually objected that alkalies fail of effect with the majority of cases of coma. That alkalies are not curatives with many cases is doubtless true but it must be granted to advocates of the theory that the amount required is almost impossible to administer. With but one possible exception there are no fatal cases on record where the urine has successfully been rendered alkaline and in this instance the patient succumbed to the attack. The single exception mentioned is a case of Ehrman's and valid objections have been raised to this example.[13] When one considers the enormous amounts of β-oxy-

[11] Porges: Wiener klin. Wochenschr., 1911, 22.
[12] Strauss: Deut. Arch. f. klin. Med., 1913, 109, p. 3.
[13] Blum: *loc. cit.*

butyric acid that accumulates in the tissues during coma it is not surprising that alkali therapy often fails. Magnus-Levy recovered from the tissues of patients dying in coma 150 to 200 grammes of oxybutyric acid; an amount which if reckoned per kilo body weight is as much as Walter used to induce coma in rabbits. In order to neutralize this and effect its elimination there would be required 200 to 300 grammes of bicarbonate of soda. Moreover, in this state the production of acids goes on constantly. A case of Magnus-Levy, a boy weighing but 30 kilos, recovered from coma after having received about 200 grammes of soda bicarbonate during 24 hours. The total ketone elimination in the urine during this day was 160 grammes. As Blum has said, the failure of alkali therapy to cure is quite as much in support of the acidosis theory as against it so long as enormous dosage does not result in alkaline urine. The crucial evidence against the acidosis theory rests on showing that cases die in coma following the successful administration of sufficient alkali to secure alkaline urine. This evidence is lacking. On the contrary there is a considerable evidence to attest the fact that even with cases that terminate fatally there is marked temporary improvement following large doses of alkalies.[14]

The acidosis theory of Stadelmann and Naunyn

[14] Hanssen: Zeit. f. klin. Med., 1912, 76, p. 219.

has not met with the approval of Ehrman, who regards the symptoms of coma diabeticum as due to the toxic properties of acids in contrast to their acid properties since the salts are alkaline. The question then arises which of the many fatty acids that might occur in this state of morbid metabolism is sufficiently poisonous to induce symptoms? Von Noorden, who has supported Ehrman's hypothesis, contends that oxybutyric acid is toxic. Of the ketone bodies acetone does not come into consideration, since it results from spontaneous breakdown of diacetic acid, which is more toxic than oxybutyric acid. When administered as its sodium salt oxybutyric acid is not more toxic than acetic acid. In his earlier paper Ehrman [15] contended that the toxic acid is butyric. When this acid is given in the form of a sodium salt to cats and puppies it induces coma, air hunger, and diminished intra-ocular pressure, characteristic of coma in diabetes. With other acids employed, propionic, valerianic and isobutyric, the effects were much less pronounced, hence Ehrman concluded that butyric is the specific acid. Butyric acid, however, has not been isolated in appreciable amounts from the urine or tissues of coma cases, and, while it might be contended that butyric acid is too easily transformed into its catabolic derivatives to be detected in the tissues, this argument in itself could

[15] Ehrman: Zeit. f. klin. Med., 1911, 72.

be used against Ehrman's hypothesis. In his most recent contribution this investigator appears to have abandoned butyric acid since observing that a typical coma may be produced in rabbits by means of oxybutyric combined with diacetic acid. This coma he believes due to the toxic properties of these acids since the symptoms noted depend on the amount of acids in relation to the weight of the brain rather than in relation to body weight.[16] Considering the numerous sources of possible error in experiments conducted in this manner one cannot be deeply impressed with the finality of the results. Ehrman's hypothesis may be true but it rests at present on insecure foundations.

There are two sources of weakness in the acidosis theory of coma; one is that the acids concerned exist in the tissues, we must assume, not as free acids but as salts in combination with sodium, potassium, ammonium, etc., but these salts are not acid but possess alkaline properties as Ehrman pointed out. The second weakness in the theory is that the blood in cases of diabetic coma does not invariably show preponderance of hydrogen ions. The blood is not less "alkaline" than normal. Of eleven cases examined by means of the electrochemical method Rolly [17] found the H ions increased in but three. If further investi-

[16] Ehrman: Berlin. klin. Wochenschr., 1913, No. 2, Jan. 13.

[17] Rolly: Mediz. Klinik, 1913, IX, Apr. 13. Münch. med. Wochenschr., 1912, 59, p. 1201.

gation substantiates Rolly's observation some changes in our conception of coma will be imperative. There is room for a conception of acidosis that has not been touched upon. The distinction between whether an acid is injurious because of its inherent toxic properties or simply because it is an acid becomes a very nice one when we deal with acids the salts of which are not themselves poisonous. It is conceivable that an acid not toxic in itself nor forming salts which are toxic might produce toxic effects nevertheless. It is well known that in the fluids of the body there is a certain relation maintained between the various bases, sodium, potassium, etc. In effect the withdrawal of one of these is equivalent to a surplus of bases left. Dennstedt [18] found in the ash analysis of blood and tissues of diabetic cases less sodium than normal, and this fact is the more striking since large amounts of sodium bicarbonate had been administered to these patients. The potassium was increased. These results suggest a selective action on the part of the acids for a certain base, sodium, which in effect and actually results in a preponderance of others. It is possible that in the disturbance of some delicate adjustment such as is this will be found the explanation of those cases of coma that do not show an excess of hydrogen ions in the blood.

[18] Dennstedt: Mitteilung aus d. Hamburg Staatskrankenanstallten, 1900, 3, 1; Zeit. f. klin. Med., 1905, 58, 84.

X

RENAL DIABETES

THERE are on record a number of cases of glycosuria attributed to increased permeability of the kidney—renal diabetes. The features that first attracted attention to this anomaly and suggested that the disorder is not a true diabetes are that the amount of sugar excreted is but little or not at all influenced by the amount of carbohydrate ingested; and also that these individuals present none of the typical diabetic symptoms. A more careful study of these cases has also disclosed the fact that the amount of blood sugar is within the physiological limits—not over 0.1 per cent. A certain conservatism, if not skepticism, prevails regarding the nature of these cases of so-called renal diabetes, and under close scrutiny but very few of those recorded can escape the suspicion that they are early manifestations of diabetes mellitus. The ultimate criterion according to our present knowledge is the blood sugar and until recently the methods of analysis gave ample chance for error in these estimations. Two cases that meet with the necessary requirements for differentiation may be cited. The first, reported by Bonniger,[1] is that of an alcoholic

[1] Deutsch. med. Wochenschr., 1908, p. 780.

man thirty-seven years of age. The sugar excretion of 0.2 per cent. on an ordinary diet was not influenced by the strictest carbohydrate-free diet, neither was it influenced by the addition of 100 grammes of glucose to a diet rich in starch. In addition it was found that the glucose excretion bore no relation to meals. The blood analyses showed that the sugar varied from 0.097 to 0.062 per cent., while the urinary excretion of glucose fluctuated from .2 to .5 per cent. Tachau's case entered the hospital on account of diarrhœa. The sugar excretion was always less than one per cent. and at times this disappeared on ordinary diet. There was no increase of sugar elimination after ingesting 100 grammes of dextrose and hyperglycæmia was not found throughout the period of observation.[2] More recently a renewed interest has been awakened in the subject on account of the relation it holds with some cases of glycosuria during pregnancy. The frequency of sugar excretion during this period has been remarked by numerous observers, notably von Jaksch and Bergsma. Naunyn regarded the condition as pathological and Hofbauer believed the fault depended on hepatic function. A more careful study of these instances of pregnancy glycosuria has disclosed that while with a small percentage the sugar excretion represents the inception of true diabetes,

[2] Deut. Arch. f. klin. Med., 1911, 104, p. 448.

with the majority this is not the case. The glycosuria may recur during several pregnancies while during the intervals the urine is normal. Moreover the sugar excretion presents all of the characteristics that connote renal diabetes: the amount of sugar excreted is relatively slight, 6 to 15 grammes per day, and varies considerably irrespective of the diet and there are none of the symptoms associated with true diabetes. The blood sugar is normal or low.[3] The explanation that has been suggested is that the renal cells are hypersensitive to glucose.[4]

[3] Mann: Zeit. f. klin. Med., 1913, 78, p. 488. Frank: Arch. f. exp. Pathol. u. Pharmakol., 1913, 72, p. 387.

[4] Novak, Porges, and Strisover: Zeit. f. klin. Med., 1913, 78, p. 413.

XI

DIAGNOSIS AND CONSIDERATIONS WHICH AFFECT THE COURSE OF THE DISEASE

THE significant feature of diabetes mellitus is a glycosuria which is constantly present on a normal diet. Glycosurias due to excessive amounts of food, to alcohol, and many other causes that have been already referred to are excluded from the category of diabetes by the transitory nature of the sugar excretion. Doubtless many instances of intermittent glycosuria represent an initial stage of diabetes, but on the other hand, it is equally certain that all do not. With regard to the class of persistent glycosurias, diabetes, it seems most probable that there we meet only a single common symptom, the sugar excretion, dependent on several causes. Certainly the clinical picture of diabetes in a child with its fearful rapidity and the almost immediate development of acidosis leading to death in a few months has very little in common with the slow benign course of the malady in elderly adults. Other discrepancies in the unity of the disease have often been emphasized and classifications have been suggested but none has withstood criticism. Tests that we may apply during life are lacking and

morbid anatomy fails to disclose a constant etiology. Until these deficiencies in our knowledge are filled we are forced to group together—because of certain similarities in symptoms and a few constant signs—several disease types.

While it may not be evident at once with every case what the course of the diabetes will be, a little study and observation is usually sufficient to enable one to assign an individual case to certain broad groupings without respect to the etiological factors involved so much as with regard to the course and progress of the disease.

With children and young adults the progress and termination of diabetes may be seen definitely. The children all succumb within a comparatively short period after the disease is recognized; two years from the time of the first symptoms is the longest tenure that has come to my observation. I have known of no case of recovery. Naunyn mentions a four year old girl who for a period of three weeks (November 27 to December 13) excreted two to five per cent. of glucose. No sugar was ever found subsequently and the child grew to a healthy woman. The attack of glycosuria followed acute gastritis. Naunyn cites this case with all reserve and does not seem to regard the recovery as due to any therapeutic means employed. These instances are of such excessive rarity that they

extend no ground for optimistic prognosis. The prognosis in regard to length of life with adolescent individuals is very uncertain for these reasons: In the beginning, the disease is often but moderately severe, occasionally even light; the glucose may vanish with strict diet or is controlled to a small daily output; there is no acidosis and it is not difficult to maintain good nutrition. This condition of affairs may persist for months without change and the family, and perhaps also the physician, are deceived by appearances. Sooner or later, however, there comes a change and this change is often very sudden. The glycosuria is now severe and is difficult to influence by diet and what is worse the urine gives the reactions for ketone bodies. In a word the patient has developed the severest type of diabetes. From this time on it is a death struggle with acidosis. It is impossible to foresee how long a period will elapse before this latter final stage of the disease becomes manifested. With some cases it is five or six years, with others only a matter of months. Since prolongation of the less severe period is influenced considerably by watchful observation and appreciation of the significance of seemingly trivial details in the urine analyses and the condition of the patient, too much emphasis cannot be placed upon their necessity. The advent of the second or severe phase leaves only too little that may be done

to lengthen life. With many, however, the disease is not recognized until acidosis is pronounced and the end already in sight. Of the cases of diabetes before the second decade, with the great majority death is due to coma. Coma has been the direct cause of death of all of the cases of this class that I have treated or seen in consultation. In some instances the fatal acidosis was aggravated by slight infections, such as tonsillitis, influenza, and in one case by measles. It is also to be noted that the sugar excretion with these individuals increases during the period of an infection which is in contrast to the findings with milder types of the malady. The relation of comparatively slight intercurrent infections to the diabetes is often remarkable. The fact that these patients are prone to infections is well known, but what is referred to here is the effect of the febrile period on the diabetes and this is especially manifest with young persons. It happens quite often that following a sharp attack of influenza or tonsillitis there is noted at once a marked increase in the sugar output and upon investigation it is discovered that the patient can no longer utilize the same amount of carbohydrate that he did previous to his fever. With the smaller fraction of the cases careful regulation of the diet may restore the lost ground, with many the loss is irreparable. This is often the crucial period when a diabetes heretofore tractable takes on its worst

aspect. When the disease is already well advanced and there is acidosis, even though the latter may be slight, then any infection becomes a grave danger. Because of the loss of appetite and fever the patient loses weight rapidly. Even when there is reserve enough to combat the infection the danger of coma besets the convalescent. These considerations apply to all of the severe cases of diabetes but the relations are closest when the patient is young.

In proportion as the patient is older the course of the disease tends to be less rapid and the acidosis less of a menace. While there are exceptional cases even in advanced life that progress rapidly to fatal coma, the first statement represents the consensus of experience. Even with severe diabetes in adults the period of life that may be expected is longer than when the disease develops during adolescence. On account of their impoverished nutrition these patients are specially prone to serious infections. The hospital patients with severe or moderately severe diabetes usually present evidence of pulmonary lesions if the primary disease has been of any duration. On the other hand, in private practice I have seen but four cases with complicating tuberculosis—an exceptionally small percentage I imagine. The two diseases may advance with fearful rapidity to a fatal termination. Pneumonia claims many cases of diabetes either directly or through se-

quelæ. It is a common end with the milder forms of the disease.

A few cases of severe diabetes develop a true parenchymatous nephritis, and in one instance at least, I have been convinced that the terminal coma was uræmic and not diabetic. It is possible that this termination is less rare than is generally supposed; convulsions at any rate should always excite suspicion.

In striking contrast with these rapidly developing, and one might say, malignant types of diabetes is the manifestation of the disorder in individuals past the meridian of life. It does happen that in advanced years diabetes may be of a severe type; but this is the exception. Almost every physician knows of a man who has had constantly in his urine for years one or two per cent. of sugar, whose diet has been a mere farce and yet fair health and activity have been preserved. A few of these doubtless live to be sixty or sixty-five years of age and never know any of the serious complications of their disorder. Some annoyance from polyuria, a little eczema are the extent of their troubles. A woman whom I saw in her later life had had a constant glycosuria for over fifteen years, and not till she was past seventy did there appear any serious complication, in this instance cataract, for which the diabetes could be assigned as a cause. She had consulted many physicians and usually ate

candy ("just one piece") with after dinner coffee! Another similar case was that of a man fifty-eight years old who was sent to me on account of perforating ulcer in the foot. He said he had been refused life insurance when he was about forty on account of glycosuria. His dietetic restriction had consisted in using gluten bread instead of white bread. He frankly confessed no confidence in diet other than a liberal one and demanded, like Moliere's hero, a pill. He was thin but hale and had no significant symptom other than the one mentioned.

These cases, however, cannot be regarded as the average nor is it ever safe even in advanced life to belittle a real diabetes. The majority do not escape penalties when they disregard their disorder, and the prognosis with those in the earlier years of the disease depends not only on how easily the glycosuria responds to curtailment in diet but also on the ability of the patient to control himself and his surroundings. With poor patients where dietetic demands cannot be met, where the occupations expose them more or less to minor injuries which easily become infected, and with whom sanitary surroundings are not the rule the prognosis is much worse than in the case of the well-to-do. The complications are more to be feared than the disease. Of diabetic patients over fifty years of age who were treated in the wards or clinic of New

York Hospital, I found that two deaths occurred from surgical complications to every one in the medical wards. The surgical diseases were infections either primary or secondary to some injury.

A sequence of events which has come to my attention repeatedly in cases of long standing is associated with the disappearance of sugar from the urine. The explanation assigned for this disappearance of sugar is that there is a secondary nephritis on account of which the kidney becomes less permeable to glucose. In support of this conception is the sequence above referred to—a diabetes of mild type which, having existed for years, has first become intermittent and finally vanished so that with a normal diet no sugar is excreted. Even before the sugar is gone there is some increase in the blood-pressure, 170 to 180 mm. mercury, and not infrequently vague cardiovascular symptoms. These patients are also prone to neuritis. The disease picture from this time on is that of chronic nephritis and arterial sclerosis. Of four such cases (three men and one woman) one died of cerebral hemorrhage, one of uræmia, and two of cardiac dilatation— in all four the modes of death were those of hypertensive nephritis. In one of these cases I examined the blood for glucose and found 0.19 per cent., which throws no light on the diabetic condition, as increased

blood sugar is not infrequently found with renal disease where there is no history of diabetes.

Diabetes in middle life is almost invariably attended by a demonstrable hardening of the arteries which is directly responsible for many symptoms. Among the serious consequences of this arterial change is peripheral gangrene, commonly of the toes or foot, rarely of the fingers. This necrosis very often commences in a trifling abrasion or bruise which becomes infected and by extension involves the structures and periosteum, until there is a large area of dead and sloughing tissue. The condition is always very serious and surgical measures disappointing. It too often happens that a low amputation is followed not by healing, but by a new area of necrosis, requiring a second higher amputation and so on until the exhausted patient succumbs. Surgical treatment is almost hopeless unless it is accompanied by intelligent control of the diet and often the latter will obviate the need of radical measures.[1]

The course and hence the prognosis of many of the surgical complications that arise with diabetes depend in a large measure upon the success in treating the diabetes. It is true of carbuncles and phlegmonous conditions generally that after the necessary operation the wound is sluggish and reparative processes

[1] Lambert and Foster: Annals of Surgery, Feb., 1914.

abeyant until attention is directed to the dietetic treatment. The results are then sometimes astonishing in the rapidity of convalescence. When the patient is old or much undermined by the primary disease these infectious processes are terminal.

With regard to those glycosurias that accompany gout, " gouty diabetes," the vast majority are not diabetes at all, since the sugar excretion is not constant. The typical glycosuria of gouty subjects is alimentary; sugar can be detected in the urine voided a few hours after dinner and not at other times during the day. Moreover, the glycosuria vanishes as soon as the total food quantity is reduced to proper amounts. The condition has come to my attention repeatedly in large robust individuals who are heavy feeders and have experienced one or more attacks of typical gout. In a small percentage of diabetics, according to von Noorden, 3 per cent., there is complicating gout. Unless the former disease is of a severe type the prognosis depends essentially on the gouty factors—nephritis and arteriosclerosis.

In conclusion then the factors which are of chief moment in determining the prognosis are: (1) The age of the patient. In youth all that may be expected is to prolong life somewhat. With adults and in middle life treatment may hold the disorder in check for indefinite periods. (2) The type of diabetes; the

outlook is improved just in proportion as the tolerance for carbohydrates can be increased. (3) With cases where there is a low tolerance for carbohydrates and where treatment fails in establishing an improvement in the tolerance, acidosis is sure to appear. The degree of acidosis governs the term of life for the patient. (4) The social status controls in a large measure the consideration that the patient is able to give to his disorder.

XII

TOTAL METABOLISM IN DIABETES

For the intelligent care of cases of diabetes an understanding of the metabolism of the diseased state is requisite. Not only is there found in this disease a loss of nourishment through the urine which must be compensated for but the failure of the cells to utilize in a normal degree the nutrient substances presented to them results in various deviations from normal which require attention and insight.

It is a well-known fact that the diabetic loses weight; in severe cases this loss over a period of time may amount to a considerable fraction of the body weight. Even in brief periods, a few days, there is often to be noted with severe cases a loss or gain of four or five pounds which is not infrequently a source of error in interpretation. Slight fluctuations are normal in health, and with this disease these are much magnified. The gain of a couple of pounds often observed following a day or two of oatmeal diet or the administration of moderate doses of alkalies cannot be translated to mean an increase in body tissue. It is properly a retention of water. This phenomenon is observed chiefly with the more severe diabetics where there is some acidosis. In exceptional instances the

use of alkalies may effect sufficient water retention so that palpable œdema is manifested. On the other hand, sudden losses in weight may be due solely to loss of water. Bischoff and Voit observed a half century ago that with a diet chiefly composed of carbohydrate there is a retention of water and in more recent experiments [1] it has been shown that when with normal men the carbohydrate of the diet is largely replaced by fat there resulted an average loss of 900 grammes of water per day for three days—nearly six pounds. There is something in the nature of a rich carbohydrate diet that normally causes retention of water and when the carbohydrate is replaced by fat and protein the tissues release the fluid. When with cases of diabetes the carbohydrate ingest is sharply reduced there is often to be observed a loss in weight during the first few days of the new diet which is explicable entirely as a loss of water. Even with severe cases this rate of loss does not persist over long periods. If it be borne in mind that about 60 per cent. of the body is water it then becomes evident that slight fluctuations in the percentage of water accrue to considerable gains or losses in weight. In order to explain persistent fall in weight over long periods of time we must look to actual tissue loss; and of the

[1] Benedict and Milner: U. S. Dept. Agr. Office Exp. Stats. Bul., 175, 1907, p. 225.

constituents of the body—protein, fat, and carbohydrate,—it is the fat that largely suffers depletion. The amount of carbohydrate in the body is relatively small, ordinarily about 400 grammes of glycogen, and the loss of a large part of this would effect only a trivial fall in weight; moreover, as the organism alike in health and disease conserves its protein, it follows that tissue loss must be at the expense of fat. When the fat depots are exhausted there may be an inroad upon the more vital tissue, protein.

With normal man at rest there is a constant demand of energy for the maintenance of body temperature, the muscular work of the heart and various cellular processes such as digestion; this demand amounts in adults to from 30 to 32 calories per kilo body weight per day. Since the diabetic organism fails more or less to make use of one of the chief sources of energy in health, sugar, the question arises as to the sources of the necessary energy in this disease. Also the question must be answered as to whether the total metabolism is in amount different or the same as in health.

Fat and carbohydrate contain the elements carbon, hydrogen, and oxygen and the resultant products of oxidation are CO_2 and H_2O. With protein there is the additional nitrogen which is excreted in the urine as urea, ammonia, etc. Hence a measure of the total

tissue metabolism is found in the estimation of the carbon and nitrogen excretion.

First with regard to the nitrogen metabolism. With normal individuals the nitrogen excreted in the urine during periods of fasting averages about 6.8 milligrammes per kilo per hour. With diabetic patients this figure tends to be higher, according to Benedict and Joslin,[2] 8.4 milligrammes per kilogramme per hour as an average and with individual cases somewhat more. This increase is not held to be a specific action of some factor in the morbid state upon protein but rather as one of the compensatory measures for the carbohydrate deficit.

There are several methods of investigating the carbon dioxide excretion and oxygen absorption and results vary slightly, depending on whether the chamber calorimeter is employed or the respiration apparatus of Zuntz. In the absence of better evidence an average of the results obtained by the two methods with the same diabetic patients may be cited. Benedict and Joslin found the carbon dioxide production for severe diabetes amounts to 3.33 c.c. per kilogramme of body weight per minute; while with normal persons it is 3.13 c.c. This means an increase of approximately 6 per cent. with the diabetic. The rate

[2] Benedict and Joslin: A Study of Metabolism in Severe Diabetes. Carnegie Institute, Washington, 1912, p. 102.

and amount of oxidation in the body can also be measured by using as an index the amount of oxygen absorbed. By some the oxygen consumption is regarded as of greater significance in measuring the caloric output than is the carbon dioxide production. The oxygen consumption with normal men is 3.75 c.c. per kilogramme per minute and with severe cases of diabetes 4.54 c.c.[3] Even higher figures have been noted by Rolly[4] and by Leindörfer.[5] Using these figures as an index Benedict and Joslin conclude that the metabolism in severe diabetes is from 15 to 20 per cent. higher than normal. Translated into terms of heat units this would mean that whereas the normal person at rest requires about 32 calories per kilo body weight cases of severe diabetes utilize 37 to 38 calories. This conclusion is not in harmony with the results of other investigations. It has been the belief that the energy requirements in diabetes are about 5 per cent. above the normal. DuBois and Vedder[6] found the requirement 31.7 calories per kilo for mild and 34 calories for severe cases of diabetes, results that are in accord with the older investigations.[7] Benedict and

[3] Benedict and Joslin: *loc. cit.*

[4] Rolly: Deut. Arch. f. klin. Med., 1912, 105, p. 494.

[5] Leindörfer: Biochem. Zetschr., 1912, 40, p. 326.

[6] Arch. for Intern. Med., 1910, v, p. 37.

[7] Magnus-Levy: Von Noorden's Handbuch d. Pathol. d. Stoffwechels, 1906, p. 291.

Joslin believe the heightened metabolism is connected with acidosis since it was found that by inducing acidosis in normal men with diets poor in carbohydrate there resulted here also an increase of carbon dioxide excretion and oxygen consumption.

The carbon dioxide production and oxygen consumption not only serve as a guide to the amount of energy produced but they may also be used to indicate the character of the catabolic process. That is to say, the respiratory quotient indicates whether fat, carbohydrate, or protein is undergoing oxidation in the tissues. The respiratory quotient is derived by dividing the volume of carbon dioxide produced by the volume of oxygen consumed $\left(\frac{CO_2}{O_2}\right)$. For the oxidation of one molecule of glucose to CO_2 and H_2O six molecules of oxygen are necessary, and there result six molecules of carbon dioxide plus water and the respiratory quotient is then one.

$$C_6H_{12}O_6+6O_2=6CO_2+6H_2O$$

$$\text{R.Q.}\ \frac{6CO_2}{6O_2}=1$$

Egg albumen will serve as a typical protein and derives a respiratory quotient of 0.8.

$$C_{102}H_{160}N_{26}O_{32}S+107\tfrac{1}{2}O_2 = 89CO_2+54H_2O+13CO(NH_2)_2+SO_3$$

$$\frac{89}{107.5}=.82$$

With suitable apparatus it is possible to measure the oxygen consumed and the carbon dioxide produced during any given interval of time, and from these results then it may be definitely ascertained whether either carbohydrate, fat, or protein is being metabolized. When the body is burning mostly carbohydrates the respiratory quotient is near one; on the other hand, when fats and proteins are being consumed the quotient is something over 0.7. Now in the first place this quotient offers a means of detecting whether the diabetic organism can burn carbohydrate, for if the quotient is not raised following the ingestion of this food it follows that the sugar is not catabolized. With diabetes it is found that the respiratory quotient is lower than normal, ranging, according to different observers, from 0.66 to 0.76, and that the lowest quotients are found with the most severe cases of the disease. Benedict and Joslin[8] recorded 0.74 for severe cases and 0.76 for light cases of diabetes; and Rolly[9] noted much lower results for severe cases. A quotient that is 0.74 or lower indicates that the body is consuming chiefly fat. The slight rise over the quotient for purely fat combustion of 0.71 is due to the metabolism of small amounts of protein; and a fall below this figure is caused, as Magnus-Levy pointed

[8] *Loc. cit.*, p. 111.
[9] Deut. Arch. f. klin. Med., 1911, 102, p. 494.

out, by the incomplete fat combustion manifested in the excretion of ketone bodies in the urine. The net result then of studies of the respiratory quotient indicates that the metabolism in severe diabetes is primarily fat metabolism in contrast to normal, which is primarily one of carbohydrate.

There is not a sufficiency of data bearing on the influence of muscular work upon the quotient in severe diabetes to give basis for definite conclusions. With some cases the quotient is lowered indicating perhaps a relative increase of fat over the protein factor in catabolism. With other cases there has been observed a rise in the quotient which might be interpreted to mean a combustion of stored carbohydrate (glycogen). That the severe diabetic can burn small amounts of reserve glycogen under stress of work is possible and the idea has been advanced as an explanation for the increased acid production that some cases manifest following exertion. This explanation is based on the assumption that the glycogen stores inhibit acidosis; as these stores are depleted acidosis increases. If this be correct the acidosis following acute infections in diabetic subjects can be explained on the same basis, the glycogen stores are exhausted during the febrile period.

Thus far then it appears from a study of the

metabolism that in proportion to the severity of the disease there is a decrease in the ability of the tissues to utilize sugar. Sugar normally saves protein and fat to the body by being given preference as fuel in the tissues, or, as it is commonly expressed, sugar is a protein sparer. When the sugar is not utilized there is increased catabolism of protein and fat and this is evidenced in the respiratory quotient and the nitrogen excretion.

The sugar of the body is derived from two sources: from carbohydrates, ingested or stored as glycogen; and from protein, either of food or tissues. In severe diabetes the sugar derived from protein is also excreted unburned; hence it may be possible to estimate in some cases the severity of the diabetes from the dextrose-nitrogen in the urine. As noted already this ratio is a nearly constant quantity in dogs after total removal of the pancreas and after phlorhizin. With a diabetic man Mandel and Lusk [10] secured a dextrose-nitrogen ratio of 3.6 which would indicate that all of the sugar derived from protein was being excreted in the urine and none burned and hence this ratio was called the fatal ratio. Since this observation a number of investigators have reported cases of diabetes where the ratio was much higher than 3.6 to 1 and have

[10] Deutsches Arch. f. klin. Med., 1904, 81, p. 472.

endeavored to prove from this that sugar must be derived from fat as well as protein. The error common in these experiments has been that the diet was not sufficiently controlled. While it is theoretically possible that sugar may be derived from fatty acids the fact is wholly undemonstrated. Using as a subject for experiment a man with the severest type of diabetes and with coma symptoms requiring infusions of alkali Foster [11] found a ratio of 3.4–3.6 for 3 days during which the diet was exclusively meat and fat.

From the point of view of available energy the diabetic might live indefinitely on a diet of meat and fat. The condition is purely that of substituting one energy yielding substance for another. With severe diabetes, however, there comes a time when fats are but incompletely utilized and this is marked by the excretion of the partly catabolized products, the ketone bodies, in the urine. This may be no inconsiderable drain upon the struggling organism as each gramme of β-oxybutyric acid means a loss of 4.4 calories, that is an excretion of 50 grammes of oxybutyric acid represents 220 calories. In the condition of total diabetes where the sugar derived from protein is not burned the ruinous economic state is revealed clearly in figures. If there be an excretion of 15

[11] Foster: Deut. Arch. f. klin. Med., 1913, 110, p. 501.

grammes of nitrogen in the urine this represents 94 grammes of catabolized protein (15 × 6.25); the heat value of which is 374 calories. From this protein then is derived 54 grammes of sugar (15 × 3.6) equal to 221 calories or 58 per cent. of the total heat value lost. If in addition the butyric acid derived from the amino-acids is not burned but excreted in the urine the loss is even more.

XIII

TREATMENT

In the majority of cases the presence of sugar in the urine is attended by so few urgent symptoms threatening life, or even efficiency, that physicians too often are content with the slightest attempts to restore a more normal condition. For example, it has required considerable reiteration to awaken a realization that the percentage of sugar in a single specimen of urine really gives no indication whatever concerning the patient's disease. A low percentage has been regarded as negligible and only with the advent of complications is there an effort made toward treatment. It has become an old story on seeing cases in coma to be informed that the sugar had never been over two per cent. A complete twenty-four hour specimen later sometimes measures over five litres and discloses a new significance to percentage. While it is doubtless true that some cases of diabetes that develop in later life run a mild course and live out the allotted three score and ten, yet we are at present unable to differentiate these individuals from the less fortunate ones who suffer from numerous complications. Now since it has been repeatedly shown that of the latter class the

majority can be rid of the distressing and dangerous elements in their disorder by suitable treatment, then it seems more than probable that had proper care been exercised the complications would not have arisen.

A small percentage of the cases of diabetes may be separated from the whole on account of the prominence of some specific disorder in the clinical picture requiring special treatment and this disorder generally relates to the gastro-intestinal tract. Dietrich found a catarrhal gastritis in 67 per cent. of his cases. Occasionally treatment directed to the gastritis is beneficial also to the diabetic condition. A number of such cases have been reported by Funk [1] where the treatment of achylia gastrica, or colitis has apparently raised the sugar tolerance of the patient to a very large degree. I have also met with instances of well marked gastritis but I have not been fortunate in producing any essential change in the diabetic state by gastric lavage as advised by Dietrich and others. It has even been claimed that with some cases so treated the sugar disappears from the urine even on a normal diet, that is, the patient is actually cured. With suitable cases the procedure is worthy of trial since for no other measure at our command can a like claim be substantiated.

There have been reported several cases where the

[1] Medizinisch. Klinik., 1912, VIII, No. 33.

sugar has disappeared from the urine following the removal of a tumor—hysterectomy for carcinoma, prostatectomy on account of hypertrophy. These instances are excessively rare and we have no explanation for the phenomena mentioned. For the vast majority of cases the only therapeutic agent that yields any degree of success is diet.

The problem presented in each diabetic individual is: How much sugar can he utilize? The answer to this question is important since if a surplus over the amount which can be cared for by the tissues be ingested, not only is that excess excreted but the ability of the tissues to use sugar is gradually diminished; or as Hoffman stated the principle for all physiological activities:—Overstrain weakens while rest strengthens any damaged function. In diabetes we have to do with an impaired function, the tissues are not able to make use of sugar as a source of energy, nor can sugar be warehoused as glycogen. These functions are completely lost only in the terminal stages of the very severe cases, in all, however, they are in some degree below normal. Dietetic treatment has for its object the regulation of the demand made upon this function so that there may be opportunity for recuperation, *i.e.*, an increased ability to metabolize carbohydrate. This is the governing principle and all methods, no matter

on what theory of etiology nor how devious, are efforts to this end.

Since the demands made upon the body to use carbohydrate are to be limited to its capacity it follows that some method must be employed in the first instance to test this function in each case presented. In order to do this a standard diet of known composition is given the patient, then the urine analyses enable the observer to estimate with some degree of exactness the amount of carbohydrate actually metabolized by this patient. Because it is not advisable to eliminate at once all of the carbohydrate from the diet it is customary to incorporate in this test diet a small known amount of starch. For convenience it is advisable to use a starch preparation that is fairly constant in composition and since breads are very inconstant a standard biscuit is preferable. The following diet has been found satisfactory although it has nothing of special merit other than that the composition is known approximately.

"TEST" DIET

Breakfast:

3 eggs with 25 gm. of bacon.
3 biscuits (Huntley and Palmer "Breakfast")[1] with 20 gm. of butter.
1 cup of strong coffee with 25 c.c. of cream.

[1] The biscuits have been analyzed at intervals in my laboratory and found approximately constant in starch content. Each biscuit contains from 4.87 to 5.13 grammes carbohydrate.

Dinner:

1 cup of bouillon.
150 gm. of beefsteak or roast beef (weighed cooked).
Boiled cabbage or cauliflower with butter sauce *ad libitum;* lettuce with oil and vinegar.

4 to 5 P.M.:

Coffee or tea with 25 gm. of cream.
1 biscuit, 10 gm. of butter.

Supper:

100 gm. of fish (weighed cooked).
2 eggs.
Asparagus as salad or hot (with butter sauce).
3 biscuits; 20 gm. of butter.
1 dozen almonds.

This "test" diet contains from 50 to 55 grammes of carbohydrate (estimated as glucose) and about 16 grammes of nitrogen (16 x 6.25 = 100 grammes protein). It is necessary to use a "test" diet for at least two days as there is, during the first twenty-four hours, an excretion of sugar representing that formed from the food consumed before the diet is begun.[3] The twenty-four hour collection of urine for the second day of the test diet must be examined with care in order to learn the facts which determine the future treatment of the case. In addition to quantitative estimation of the glucose the urine must be tested for diacetic acid and if the latter be present the total ammonia should be estimated as a guide to the degree of acidosis. The determination of the total nitrogen

[3] The total carbohydrate value of the diet should include the glucose available from the protein. This latter would amount to 58 gm. (16 × 3.6 = 57.6), hence the total available glucose is 108 gm. (58 + 50).

is advisable since it enables one to form a more accurate estimate of the severity of the diabetes as will be seen. It is customary to classify cases of diabetes somewhat crudely into mild and severe types of the disease; and these terms take into account the whole clinical picture as well as the result of analyses of the urine after standard diets. It is apparent that the degree of severity of the disease depends upon the ability preserved to utilize sugar in the body. This point may be illustrated by examples: if a diabetic individual be given the "test" diet and excrete 30 grammes of sugar then it is evident that he retains the function of utilizing some sugar, in this instance 78 grammes. He has metabolized some 20 grammes of sugar from starch (since the diet contains 50 grammes of carbohydrate in that form) and all the glucose from protein, 58 grammes. On the other hand, if the urine under the same diet restriction contain 80 grammes of sugar then we may conclude no sugar from starch has been metabolized and of that derived from protein only 38 grammes have been retained to the body. These examples mark a distinguishing feature in differentiation of the disease; in the first, carbohydrates are still utilized though in a restricted degree, in the second the body fails not only to metabolize sugar from starch but also fails to retain a part of the glucose from pro-

tein. The first condition would represent a mild diabetes and the second one of moderate severity.

Lusk and Falta have suggested a means of more accurate expression of the various grades of diabetes, by a quotient, and at the same time bridging the difficulties of comparison of various cases treated with different diets. This quotient is:

$$\frac{\text{Grammes of urinary sugar} \times 100}{\text{Grammes of N} \times 3.65 + \text{grammes sugar ingested}}$$

$$\frac{30 \times 100}{14 \times 3.65 + 50} = 29$$

$$\frac{80 \times 100}{15.5 \times 3.65 + 50} = 75$$

Applying this formula to the first case cited the quotient is 29 and in the second case 75. Total diabetes wherein no sugar at all is metabolized would present a quotient of 100. For the employment of this formula it is necessary to know the total nitrogen of the urine. The advantage in its use is that an index is obtained which is more definite than the vague terms mild and severe.

The results of the analysis of urine after the use of the test diet enable us to classify cases for therapeutic measures. The analysis will fall into one of the following divisions.

1. Sugar less than 50 grammes; ketone bodies absent.

2. Sugar more than 50 grammes; ketone bodies absent.

3. Sugar more than 50 grammes; ketone bodies present.

The first classification embraces the milder grades of the disorder where some carbohydrate is still metabolized in the body and where there is no acidosis. The following history is that of a case of this type.

Mr. W. R., Savannah; age forty-nine. Patient had a brother who died of diabetes, but no other member of the family has been affected. He has always been well and healthy until about a year ago and has always worked under heavy responsibilities. He has been a large eater and a moderate user of alcohol. About a year ago he felt " run down " and tired and noted that he was losing weight, and somewhat later thirst became excessive and he voided considerable urine. Suspecting Bright's disease a physician was consulted and sugar found in the urine. In consequence of abstaining from sugar and sweets the patient thinks he has improved. He is a well built man weighing 153 pounds, and presenting nothing abnormal in his examination other than a palpable liver which extends 2 inches below the costal margin in the mid-clavicular

line and does not feel rough nor unduly hard. The urine contained sugar, but no albumen; specific gravity 1032. The urine of the third day of the "test" diet is the first analysis of the table.

1911 May	Diet.	Amount. c.c.	Albumen.	Sugar. gm.	Nitrogen. gm.	Ketone. gm.
10	Test.....	1210	0	1.2 per cent. = 14.5	17.3	0
11	Test.....	1230	0	0.3 per cent. = 3.7	15.4	0
12	C. F*.....	1220	0	trace	16.1	0
13	C. F.....	1460	0	0	...	0
14	C. F.....	1440	0	0	...	0
15	50 gm. bread.	1035	0	0	...	0
16	C. F.....	1620	0	0	...	0
17	60 gm. bread.	1630	0	0	...	0
18	C. F.....	960	0	0	...	0
19	60 gm. bread.	1050	0	0	...	0
20	60 gm. bread.	1190	0	0	...	0
21	C. F.....	1080	0	0	...	0
June 1	90 gm. bread.	1370	0	0	...	0

*"C. F." in these tables signifies carbohydrate-free diet.

The notable features presented by this case are: the slight sugar excretion even while the diet contained starch; the prompt disappearance of sugar from the urine when the starch was withheld; and the rapid increase of the tolerance of the patient so that within three weeks 80 to 90 grammes of bread could be taken without glycosuria. By gradual increments the diet was further enlarged until this patient was ingesting the equivalent of 110 grammes of carbohydrate in various foods. The principle to be observed in enlarging the diet is that additions must be made gradually in small increments, keeping all the time well within

the bounds of the patient's tolerance; and second, the interpolation, at definite intervals, of strict diet days when no starch is taken. These days may be observed once a week or every tenth day and are no hardship to the patient. In this way cases of mild diabetes may be kept without glycosuria for very long periods and in excellent health.[4] With many the disease appears to have no progressive tendency. This patient has been under observation at intervals for three years and while it has not been possible to increase his allowance of farinaceous food there has been no appreciable failure in his ability to utilize the amount permitted at the end of his first treatment.

A great many cases that assume a severe character with the lapse of time are in the early stages of this bland nature. With some the disease does not progress; with others it does and I know of no way of

[4] Diabetes of even milder grades is of common occurrence. These patients are generally huge feeders who have presumed upon excellent stomachs to indulge unbridled appetites. The glycosuria is of slight degree, with little if any polyuria, and vanishes as soon as the total food quantity is made normal. These are the cases where the various advertised medicaments produce their results and purely by means of the slight diet regulations that are advised. If one case of this type, a man of forty-eight years of age, ate what he said, the carbohydrate ingest was not less than 800 grammes per day and, as his urinary nitrogen was over 30 grammes, the protein allowance was equally liberal. Allowing for a normal amount of fat the caloric value of this diet was about 4500 or some 50 calories per kilo to supply the needs of a sedentary mode of life. His glycosuria vanished without restrictions worthy of the name.

differentiating in the beginning the *mild* cases from the early manifestations of more severe disease types. The following record illustrates a transition and improvement with time.

G. S., Pittsburg, Pa., aged thirty-four. He came from a healthy family and had had no significant sickness before the onset of diabetes. He had always been a large eater and particularly fond of sweets. In August, 1911, on account of some slight digestive disturbance he consulted his physician who found sugar in the urine. Abstinence from sugar and some starch reductions in the diet resulted in the glycosuria disappearing promptly. Urine analyses were made at least once a week and no sugar was found until December, 1911. At this time the common dietary restrictions failed and the glycosuria persisted and the patient began for the first time to have some increase in the amount of urine voided. Also his weight fell from 180 to 170 pounds.

The patient began treatment March 4, 1912. With the diet he was using the amount of urine varied from 2700 to 3400 c.c. daily, containing 60 to 70 grammes of glucose. On the third day of the test diet the sugar fell to 6.7 grammes and the results of the first course of treatment are shown in the table.

Date. 1912 March	Diet.	Amount urine. c.c.	Sugar. gm.	Nitrogen. gm.	Ketone. gm.
9	Test	1920	6.70	16.8	0
10	Oatmeal	1500	7.5		
11	C. F.	800	2.1		
12	C. F.	1300	0		
13	50 gm. carbohydrate	1500	7.1		
14	C. F.	1100	0		
15	C. F.	1230	0		
16	C. F.	1180	0		
17	20 gm. carbohydrate	1210	0		
18	C. F.	1070	0		
19	C. F.	1150	0		
20	30 gm. carbohydrate	1320	0		
21	C. F.	1700	0		
22	50 gm. carbohydrate	1250	0		
23	50 gm. baked potato	1610	0		
24	50 gm. bread	1750	0		
25	C. F.	1730	0		
26	125 gm. potato	1700	0		
27	100 gm. bread and potato.	1670	trace		

The record of this case indicates an easily controlled glycosuria. His test March 9, 1912, showed that he still utilized about 40 grammes of ingested starch and the total sugar consumption was about 90 grammes. There was at no time any evidence of acidosis. During the period of treatment his weight rose from 164 to 170 pounds. He was sent home with directions to use not more than 50 grammes of carbohydrate a day, and not more than two starch-containing foods in the same day; every fourth day to be restricted and starch free. He felt himself to be in normal health and the urine contained sugar only at intervals until June, 1913. There was then some relaxation in the care he had shown heretofore in following directions and sugar was constantly

present although in but small amounts. The second period of treatment began in October, 1913.

Date. 1913 October	Diet.	Amount urine. c.c.	Sugar. gm.	Nitrogen. gm.	Ketone. gm.
24	Test.....	1160	4.6	15.31	0
25	C. F.....	1080	0	.....	0
26	30 gm. carbohydrate.....	1270	0	.....	0
27	C. F.....	1250	0	.....	0
28	30 gm. carbohydrate.....	1320	0	.....	0
29	30 gm. potato.....	1290	0	.....	0
30	C. F.....	1060	0	.....	0
November					
1	C. F.....	990	0	.....	0
2	75 gm. carbohydrate (potato and bread).....	1370	7.2	14.2	0
3	C. F.....	1100	trace	.....	0

The result of the third day of the test period showed that this patient was consuming about 100 grammes of sugar, of which 45 grammes was derived from starch and about 55 grammes from protein ($15.31N \times 3.6 = 55.08$ grammes) and this was increased to over 115 grammes on November second ($14.2 \times 3.6 = 51 + 75 = 126 - 7 = 119$). No attempt was made at this time to arrive at a higher test figure since it would not have been advisable to do so. The patient was advised to use 60 grammes of starchy food daily and to observe two days a week when no starch was taken.

The case just recorded is somewhat out of the average for the age of the patient, in that the disease was relatively bland. It seems, with some of these cases at least, as though their freedom from symptoms depended solely upon their ability and fidelity in following the advice given them.

The following patient illustrates in the history of his disease the transition of a mild into a severe form of diabetes.

S. G. E., aged fifty-four; a manufacturer, came from a family free of diabetic taint. There had been several relatives whose lives had been wrecked because of nervous diseases.

The patient first noted an increase in urine volume in 1910 and because of this he consulted his physician. The urine then contained 5 per cent. of sugar. A rest was advised but served only for transient benefit. Somewhat later there was considerable annoyance from cramps in the legs and dyspnœa on exertion. The appetite was good but easily satisfied and thirst not excessive. Examination revealed no fact other than that the patient was under weight, which was normally 135 pounds; but at the beginning of the treatment was only 125 pounds. The urinary analyses during the first period of treatment are recorded in the following table.

Date. 1911 June	Diet.	Amount urine. c.c.	Sugar. gm.	Nitrogen. gm.	Ketone. gm.
19	Liberal.....	2580	80.5	.....	0
21	Test.....	2120	36.2	16.9	0
22	C. F.....	2070	24.6	.....	0
23	C. F.....	2620	17.3	.....	0
24	Test.....	1850	0	.....	0
25	C. F.....	2050	0	.....	0
26	C. F.....	1640	0	NH_3–N 0.51	0
27	40 gm. starch (potato)....	1460	0	.....	0
28	C. F.....	2880	0	.....	0
30	100 gm. bread.....	2670	0	.....	0

Date. 1911 July	Diet.	Amount urine. c.c.	Sugar gm.	Nitrogen. gm.	Ketone. gm.
1	C. F.....	2060	0	.....	0
2	50 gm. bread and 100 of potato.....	2280	0	.....	0
3	C. F.....	2670	0	13.7	0
4	C. F.....	2430	0	.....	0
5	150 gm. bread.....	2610	0	.....	0
6	C. F.....	2020	0	.....	0
7	100 gm. bread and 1 pt. champagne.....	3050	12.20	.....	0
8	C. F.....	1680	0	.....	0
9	120 gm. starch (bread, peas, potato).....	2750	0	.....	0
10	120 gm. starch.....	.....	0	.....	0

This record shows that this patient utilized some carbohydrate at the beginning of this treatment and also that the sugar quickly vanished from the urine on a starch-free diet. An increase of the volume above normal even after the glycosuria had ceased was due to chronic nephritis. In the course of three weeks the ingest of starch was gradually increased up to 120 grammes without glycosuria. He was directed to use the equivalent of 80 grammes of starch daily excepting one restricted day each week when no carbohydrate was to be taken. The urine remained free of sugar during August and September except on two occasions when traces were noted (three examinations weekly). In October sugar appeared more frequently, on the 18th amounting to 44 grammes. The diet was curtailed but there was glucose excretion even when no starch was ingested. As the patient appeared to be losing ground he returned for a second

course of treatment in November. The result of this period shows the transition of the disease to a severe type.

Date. November	Diet.	Amount urine. c.c.	Sugar. gm.	Nitrogen. gm.	Ketone. gm.
24	Test	3400	68.2	14.6	0
25	Test	3320	59.6	15.4	0
26	C. F.	2780	46.0	15.2	0
27	C. F.	2890	41.1	NH_3—N 0.6	0
28	C. F.	3100	36.0	.....	0
29	20 gm. starch	3240	44.0	.....	0
30	C. F.	2630	29	.....	0
December					
1	C. F.	2590	19.0	NH_3—N 0.81	0
2	C. F.	2640	21.4	.....	0
3	20 gm. starch	2770	31.2	.....	0
4	Vegetable *	2610	10.6	NH_3—N 0.78	0
5	C. F.	2200	0	.....	0
6	20 gm. starch	2490	13.7	.....	0

* See page 206.

With this patient the urine could be freed of sugar only by restricting the protein food as well as the carbohydrate. During several months of treatment it was possible to bring about the utilization of only 25 grammes of ingested starch and then only when the starch days were interpolated in a manner to be discussed later. The encouraging factor in cases of this sort is the absence of acidosis and on account of the perfect metabolism of fats this food may be given in as large amounts as the digestion of the individual permits.

The failure of a rigid diet to effect a normal urine within a few days is commonly accepted as evidence

that the case is one of severe diabetes yet this is by no means always true. Very often it requires some time and perseverance to attain the desired result in patients who still have a fair tolerance. The glucose excretion with these cases is not large, 10 to 15 grammes per day with restricted diets; but often it seems almost impossible to eliminate this small amount. The following record is that of a case belonging to this category. The patient, S. R., was a banker fifty-seven years of age. He had known that his urine contained sugar for about four years. His diet during this time had not been specially restricted although sweets had been avoided. The urine had usually contained about 2 per cent. of sugar. Several months before coming to me he had a bad carbuncle. This gave him much annoyance and impaired his health, which had previously been excellent. As the wound healed very slowly his physician advised him to take a course of treatment for the diabetes. The patient was a large man who looked anæmic and pasty. Physical examination discovered a moderate degree of arteriosclerosis in his radial and retinal arteries, but nothing else of significance. He was allowed to select his own food during the first two days in the hospital and then the test diet was ordered.

Date. February	Diet.	Amount urine. c.c.	Sugar. gm.	Nitrogen. gm.	Ketone. gm.
12	Unrestricted.....	1870	66		
12	Unrestricted.....	1920	72		
13	Test.....	1780	58	18.8	0
14	Test.....	1515	45	13.5	0
15	20 gm. starch.....	1235	19.8	12.4	0
16	20 gm. starch.....	1435	8.6	12.8	0
17	10 gm. starch.....	1560	4.7	.....	0
18	No starch.....	1610	3.6	$NH_3-N=0.48$]	0
19	10 gm. starch.....	1435	4.9	12.1	0
20	10 gm. starch.....	1375	2.2	.....	0
21	Vegetable.....	1280	0	.....	0
22	10 gm. starch.....	1600	1.1	.....	0
23	No starch.....	1900	0	.....	0
24	10 gm. starch.....	1640	0	.....	0
25	No starch.....	1570	0	NH−N=0.43	0
26	No starch.....	1880	0		
27	30 gm. starch.....	1400	0		
28	No starch.....	1930	0		
March 1	40 gm. starch.....	1770	0		

Increasing amounts of starchy foods were allowed every other day until 70 grammes were being used. No sugar was found during the period of observation, which continued till March 18. The patient gained eight pounds in weight during the last two weeks of treatment. He was instructed to observe for two months longer the same routine employed in the hospital and was allowed to return home. In the course of the following ten months the diet was further relaxed so that the patient was eating daily 100 grammes of carbohydrate, as bread and vegetables. Glycosuria resulted four times in the two years following treatment, and he was well at last report.

One asks at once why should the glycosuria be so intractable in a case which proved to be of such a mild

nature. An explanation is suggested in this case in the results of the analyses of blood sugar. On February 18 this was .13 gramme per cent. and on the 24th it had fallen to 0.09; the first figure scarcely above normal and the latter below the summit of the normal variation. It might be conjectured that here we have a renal element in the picture; at least there was no decreased permeability of the kidney filter such as is frequently noticed in cases of this type resulting in a cessation of glycosuria even while there is moderate hyperglycæmia.

During the course of rigid treatment such as that presented, any intelligent patient learns a good deal with regard to the treatment of his own case. It is human nature that when the methods employed meet with success the patient loses respect for his malady, arguing that what has been done once he can do again, and the consequence often is that after he has gone from under the scrutiny of his adviser he gradually lapses into careless habits of eating. This course of events is inevitable unless the directions given permit of a variety in diet and a sense, at least, of freedom from those restraints which irk us all at times. This is the reason in a nutshell why the effects of sanitorium treatment and "cures" are apt to be of brief duration. The treatment ceases when the patient leaves the care of the physician whose advice he has sought. The

brief period of careful observation under rigidly controlled conditions is necessary in order to determine those facts on which future treatment depends. This period can and should be one of instruction for the patient on how to care for himself so that afterwards he can coöperate intelligently with his medical adviser. It is necessary then not only to insist upon the patient's help but also allowing for human weakness to furnish him with such food resources that he will not become disgusted and fatigued by monotony. The following diet scheme I have employed for a number of years with cases of diabetes where the tolerance was not so restricted as to make it impossible. It must be stated emphatically that this method cannot be used with severe cases.

As the word "unit" conveys a more definite meaning to a patient than "ten grammes" a table was constructed on a unit basis; ten grammes of carbohydrate is here expressed as one unit; twenty grammes, two units, etc. In constructing this table approximations only are considered; if a tablespoonful of a cooked food contains on analysis 12.5 grammes of starch it is recorded as one unit, likewise another food may actually contain but 8 grammes of starch; it is also recorded as one unit (10 grammes). An average is struck in the errors. As a matter of fact these approximations work out very close to actual weight as

I have found by allowing patients, whose tolerance had been tested repeatedly and found constant, to use a given number of units from the table. One patient whose tolerance was found constantly to be 80 grammes of carbohydrate was given nine units on three different occasions and there was recovered from the urine 8.7, 10.4, 7.9 grammes of sugar respectively for these three days; that is, the diet was approximately ten grammes in excess of the amount utilized and the urinary sugar disclosed the degree of approximation.

Soups.

Bean	average portion	equals	1 unit.
Clam chowder	average portion	equals	1 unit.
Cream of corn	average portion	equals	1 unit.
Pea puree	average portion	equals	1 unit.
Potato	average portion	equals	1 unit.

Vegetables.

Beans, baked	2 tablespoonfuls	equal	2 units.
Beans, butter	2 tablespoonfuls	equal	1 unit.
Beans, lima	2 tablespoonfuls	equal	2 units.
Beans, kidney	2 tablespoonfuls	equal	2 units.
Beets	2 tablespoonfuls	equal	1 unit.
Corn, canned	2 tablespoonfuls	equal	2 units.
Corn, green	1 ear	equals	2 units.
Onions	2 onions	equal	1 unit.
Green peas	2 tablespoonfuls	equal	1 unit.
Potato, baked	1 medium sized	equals	3 units.
Potato, boiled	1 medium sized	equals	3 units.
Potato, mashed	2 tablespoonfuls	equal	2 units.

Fruit.

Apple	1 medium sized	equals	2 units.
Blackberries	2 tablespoonfuls	equal	1 unit.
Cantaloupe	one-half	equals	2 units.
Currants	3 tablespoonfuls	equal	1 unit.
Huckleberries	2 tablespoonfuls	equal	1 unit.
Orange	1 medium sized	equals	2 units.
Peach	1 medium sized	equals	1 unit.
Pear	1 medium sized	equals	2 units.
Plum	2 medium sized	equal	1 unit.
Raspberries	3 tablespoonfuls	equal	1 unit.
Strawberries	4 tablespoonfuls	equal	1 unit.

Cereals.

Bread	slice 3×4×½ inches	equals 2 units.
Hominy, boiled	1 tablespoonful	equals 1 unit.
H—O, boiled	2 tablespoonfuls	equal 1 unit.
Macaroni, boiled	2 tablespoonfuls	equal 2 units.
Macaroni, baked with cheese	2 tablespoonfuls	equal 2 units.
Oatmeal, boiled	2 tablespoonfuls	equal 1 unit.
Rice, boiled	1 tablespoonful	equals 2 units.
Shredded wheat biscuit	1 biscuit	equals 2 units.
Spaghetti, baked with tomato	2 tablespoonfuls	equal 2 units.

Sample Day (6 units allowed, *i.e.*, 60 grammes starch).

Breakfast:
- Ham, eggs.
- Cereal (equal to 1 unit) with tablespoonful cream.

Lunch:
- Clear broth.
- Meat, green vegetable.
- Baked potato (equal to 3 units).

Dinner:
- Soup.
- Meat, green vegetable.
- Boiled rice (1 tablespoonful equal to 2 units).
- Salad and cheese.

Foods on the list that are not suited to an individual case are of course crossed off.

The advantage of a scheme of this character to the patient is that he is enabled to select for himself what he will eat. He is restricted only in quantity. In a surprisingly short time patients memorize the equivalents without special effort. For those cases where the tolerance is above fifty grammes the plan works well in practice. With more severe types the tolerance is apt to be too fluctuating a factor to permit of this procedure.

Finally these individuals must observe at definite intervals strict, carbohydrate-free days of diet. The object of this is not to strain, so to speak, the degree of tolerance previously established. It is to be re-

garded as a rest day for a function. In the beginning these days may be required frequently, two a week; later if all goes well, less frequently. As a rule I advise every tenth day, at least, with even the mildest cases as a carbohydrate-free day.

The second and third division of cases as determined by the urine analyses (sugar more than 50 grammes), incorporates those where there is a failure to utilize ingested carbohydrate. This failure of function may or may not be accompanied by defective fat metabolism manifested as ketonuria. Even when there is no ketonuria one must constantly bear in mind with these cases that there is this tendency and that it is much easier to prevent acidosis than it is to overcome it.

The following case, a man of thirty-six years of age, is one that appeared to be very severe but has by careful adherence to diet kept in health for four years. The patient first noted increased urination at night in 1909. At this time he was working very hard in the capacity of electrical engineer in a large manufactory. His physician told him that he had diabetes and advised that he abstain from sugar and use gluten bread. He did this and sent his urine frequently to a chemist for analysis. During 1909 the urine volume seldom exceeded two litres with an average of about 60 grammes of sugar. In 1910 he lost some weight and contracted "grip," which left him very weak. He

made a very slow convalescence and noted that he was passing more urine than previously. His physician became alarmed about him and advised him to take a course of treatment. The following table is abstracted from his record which covers nine weeks.

The result of the test diet indicates that the patient was utilizing no starch and not all the sugar derived from the protein food. The sole hopeful element in the case in the beginning was the absence of any signs of acidosis. There is not the response to restricted diet noted in the milder cases; the urine can be made free of glucose but only by restricting the protein ingest as well as excluding starch. At first this measure appeared to effect no lasting benefit since there was at once a return of the glycosuria.

Date. October	Diet.	Amount urine. c.c.	Sugar. gm.	Nitrogen. gm.	NH gm.	Ketone. gm.	Weight. lb.
19	Test 3d day.....	3300	79	23.2	.46	0	158
20	C. F.....	2780	61	19.6	...	0	158
21	C. F.....	2400	28	18.4	.57	0	157
22	Test.....	3100	68	17.5	...	0	
23	C. F.....	2580	41	18.1	.58	0	
24	C. F.....	2200	19	16.6	...	0	156
November							
6	Vegetable.....	1920	14	12.5	.68	+	
7	C. F.....	1710	0	17.2	...	+	
8	C. F.....	1820	11	17.8	.11	+	154
9	Vegetable.....	1240	0	13.1	.68	+	
20	Vegetable.....	1310	0	12.8	.57	+	154
21	C. F.....	1280	0	15.6	...	0	
22	C. F.....	1380	0	14.9	...	0	
23	Test.....	1410	31	15.7	...	0	154
December							
17	C. F.....	1370	0	14.9	...	0	
18	20 gm. bread.....	1500	trace	16.3	...	0	155
19	C. F.....	1490	0	16.8	...	0	
20	30 gm. bread.....	1370	0	14.2	...	0	155
27	Test.....	1510	14	14.9	...	0	155.5

It is evident from the latter part of the record that more starch was then being consumed by the tissues than in the beginning; in fact about 30 grammes. The patient was directed to use this routine: one day 30 grammes of bread, then a vegetable day and on the third day no starch. He was intelligent, appreciated the gravity of his condition and obeyed instructions. In the course of the next six months his condition improved so much that he resumed his work. His tolerance has never been better than about 50 grammes of carbohydrate, but with care he has preserved this and has been able to maintain fair health and freedom from disturbing symptoms.

With cases of the severer types, eliminating the carbohydrate from the diet is not sufficient to control the glycosuria. It is necessary to reduce also the protein ingested. The meaning of this is that the body is not able to utilize all the sugar derived from protein. When the carbohydrates are excluded from the diet and the protein much reduced there is, of course, an increase of fat metabolism to furnish the necessary energy for body-heat maintenance. In other words, the conditions of diet are those which induce ketonuria and since with the severe types of diabetes there is usually found some diacetic acid in the urine before the diet is curtailed it is evident that these restrictions

must be conducted with considerable care in order to avoid alarming symptoms. The following diet is one I commonly employ when protein is to be restricted:

Breakfast:

Spanish omelette of yolks of 3 eggs with tomatoes, parsley, and mushrooms.

One large cup of coffee with a tablespoonful of cream.

Luncheon:

A cup of bouillon, a large plate of asparagus with egg sauce.

4 P.M.:

A cup of coffee or a glass of wine with one casoid biscuit.

Dinner:

A cup of bouillon, 1 box of Norwegian sardines, a large portion of boiled spinach with oil or butter.

A glass of wine or whiskey and water.[5]

When this "vegetable day" is employed it is advisable to give alkalies; twenty grammes of soda bicarbonate may be given during the day with lemon juice as a palatable beverage. The object of this diet is to reduce the glycosuria by restricting the protein ingested. Its use is indicated when the glucose excretion persists in spite of a carbohydrate-free diet. There are also some cases, as has been already mentioned, where a trifling glucose excretion (5 to 10 grammes) persists, notwithstanding a restricted diet; and with these cases a vegetable day is a convenient way of hastening the desired end. It not infrequently happens that a slight degree of ketonuria first appears on vegetable days and vanishes promptly as the diet

[5] With much restricted diets it is impossible to supply an adequate caloric value. Loss in weight is for a time inevitable.

is changed. Occasionally, on the other hand, a ketonuria of decided degree drops quite suddenly following a vegetable day. With the latter cases there is always a coincident diminution in the amount of glucose excreted. The following record illustrates this fact. The patient was a young man who had been under treatment for some time before he was admitted to the hospital. The urine had, at times, contained over 100 grammes of sugar on a restricted diet. The family physician reported that there had been a positive ferric reaction for over a month.

Date. January	Diet.	Sugar. gm.	Nitrogen. gm.	Ammonia. gm.	Total ketones. gm.
14	C. F.....	68	16.4	2.7	6.4
24	Vegetable.....	11	11.4	2.9	7.1
26	C. F.....	3	15.8	1.3	4.6
30	C. F.....	5	16.1	0.8	.7

The vegetable diet in this case did not free the urine of glucose but the amounts of sugar excreted in the following days indicated that more was being consumed in the tissues and a fall in the ketone elimination is the expression of this improved metabolism.

Since with severe diabetes the acidosis demands as much or more consideration than the glucose excretion the diet has also to be arranged to meet this indication. All endeavors to combat acidosis are, fundamentally, efforts to increase the amount of carbohydrate burned in the tissues. Fats are burned in the fire of carbohydrate and our efforts are directed toward facilitating this combustion. There are two

principles involved as a result of observation: first, some starches are better utilized than others and this is true even though we cannot differentiate chemically between these starches; second, a given starch is better cared for when it is given to the body with a minimum of other food substance. The reasons for these facts are not apparent in the light of our present knowledge yet there seems no question of the validity of the facts. The application of these principles finds its expression in the rice, potato, and oatmeal "cures." With all alike, to produce the desired result it is necessary to confine the diet for a period to one of these foods. Oatmeal alone is a valuable food for decreasing ketone formation but when used with meats and vegetables its effect is much impaired. At best it is combined only with some butter fat to increase the caloric value. That oatmeal diminishes acidosis by reason of increasing the amount of carbohydrate utilized in the body is conjectured but is not adequately attested by the respiratory quotient observed after oatmeal diets when there is no decrease in the glycosuria. With some cases other forms of starch than oatmeal can be employed provided they are given in the same way, that is, in combination with a minimum of protein food. Wheat flour, for example, I have used as a porridge and as bread (bread and butter days). Before illustrating the use of these diets with specific cases attention should be directed to their limitations.

In the first place it is usually not possible to employ these carbohydrate diets for more than a few days no matter how urgent the need since patients so quickly tire of them. Then, too, the desired result does not invariably follow. Oatmeal is more apt to work well than other forms of starch but with some cases there is no resulting fall in the ketonuria with this diet and in this event other forms of starch should be tried. Occasionally starch diets induce tympanites so severe that the patient cannot endure the discomfort.

These starch diets as I have employed them are as follows:

Oatmeal Diet.

Cook in a double boiler for at least six hours ten ounces of oatmeal in two quarts of water, slightly salted. While still hot strain through a sieve and add three ounces of butter, stirring well.

This is the food allowance for one day. A cupful every two hours.

Potato Diet.

Breakfast:

One baked potato with butter.
One cup of coffee with 25 c.c. cream.

Lunch and dinner:

Potato, boiled with skin, butter.
Green vegetable, wine or whiskey.

Bread and Butter Day.

Breakfast:

Two pieces of bread or toast, buttered.
Two egg yolks cooked any style.

Lunch and dinner:

Two pieces of bread and butter.
Green vegetable with egg sauce or oil.
A rasher of bacon.
Coffee, wine, whiskey.

These diets find their chief usefulness in reducing dangerous degrees of acidosis, and since alcohol is very often an important aid to that end I commonly advise a dry wine or whiskey with soda.

In some cases (and I have observed this most frequently with children) the oatmeal diet serves not only to reduce ketonuria in a remarkable way but the glycosuria diminishes also. Several times I have seen children, with whom the sugar and ketone excretion portended a rapid, fatal issue of the disease, respond to two days of oatmeal diet by complete disappearance of the sugar from the urine. Although this result with the majority means only a postponement of the inevitable, even then it is worth while.

The application of the principles concerned with the use of these special diets is best illustrated by abstracts from the records of cases of severe diabetes. And in the selection of cases I have used only those where there was not only an obstinate glycosuria but also a more or less dangerous degree of acidosis.

The first case is that of a man thirty-three years of age, who entered the hospital in a weak and emaciated condition with the usual symptoms of severe diabetes. There was a pronounced ketonuria, which was the chief factor considered in the early part of his treatment. While the sugar output was influenced to a considerable extent the urine never became free of glucose. The degree of success with cases of this sort is meas-

ured by the fall in the ketonuria (and ammonia) and the increase in the patient's weight and sense of well being. The influence of the various forms of diet is notable. Oatmeal did not apparently diminish glucose excretion but there was a decline in the amounts of the ammonia and ketone bodies. In December a routine was advised as follows: an oatmeal day, to be followed by one when no starch was taken; then a vegetable day followed again by a carbohydrate-free day. The chart is abstracted from the record.

Date.		Amount urine.	Sugar.	Nitrogen.	Ammonia.	Diacetic.	β-oxy.	Weight.
September	Diet.	*c.c.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*lb.*
14	Unrestricted....	9050	572	28.	2.14	+	+	124
17	Test.....	4400	220*	18.	2.00	+	+	
18	50 gm. bread....	5600	308	...	...	+	+	
19	50 gm. bread....	5300	302	...	2.22	7.68	4.87	
20	50 gm. bread....	1950	121					
21	50 gm. bread....	3100	155					
22	Oatmeal.....	3200	173	12.4	1.23	+	+	
23	Oatmeal.....	3000	162					
24	C. F.....	3700	178	...	...	+	+	
25	C. F.....	1700	75					
26	50 gm. bread....	4500	201	16.4	.87	+	+	123
27	Vegetable.....	2400	72	14.2	1.82	4.03	2.17	
28	C. F.....	3200	80	...	...	+	+	124
October								
14	Oatmeal.....	2300	82	...	...	+	+	
15	Oatmeal.....	2600	91	13.2	.82	+	+	126
16	Vegetable.....	2400	77	14.8	1.23	+	+	
17	C. F.....	2700	96	...	1.14	+	+	129
November								
26	Oatmeal.....	2400	88	...	.77	+	+	
28	C. F.....	2050	59					
30	C. F.....	2140	94	...	.69	+	+	133
December								
4	C. F.....	2500	101	...	...	+	+	
6	C. F.....	3000	84	...	...	1.34	.72	
8	C. F.....	1650	52	15.7	.68	+	+	135

* When the sugar excretion is so large one suspects that food was taken that was not reported. Many severe cases are no more trustworthy than morphine habitues.

This patient remained fairly well during the winter and pursued his work. In May he contracted pneumonia and after defervescence diabetic coma supervened, from which he died.

Whether this patient's resistance to infection would have been appreciably increased by permitting us to carry out a course of treatment that would free the urine of sugar we may only conjecture. These cases—and they are numerous—represent what the patient will do for himself, not what it is possible to accomplish with severe diabetes. The following two cases adhered rigidly to the dietetic restrictions imposed upon them, with the result that the sugar disappeared from the urine and an acidosis of menacing severity subsided.

The first case is that of a man twenty-six years of age, with a history of diabetes in his family. His diabetes had been of excessive severity with rapid loss in weight and the early symptoms of acidosis. At the commencement of his treatment he was very drowsy and retained but little taken into the stomach. For thirty-six hours treatment consisted exclusively in administering alkalies (intravenously and by rectum) and whiskey (by mouth). The patient was then given small amounts of oatmeal gruel for two days, followed by two strict vegetable days (the vegetable diet of p. 206, excluding eggs and fish). On the fifth day, April 4, the diet was carbohydrate-free.

Date. April	Diet.	Amount urine. c.c.	Sugar. gm.	Nitrogen. gm.	NH_2–N gm.	Weight. lbs.
4	C.F.	2600	44.4	18.1	3.4	137
10	C.F.	2540	18.0	8.4	1.8	135
13	Vegetable	2300	0	9.1	1.4	135
16	C.F.	2225	9.1	...	0.8	
18	Vegetable	2025	8.3			
21	C.F.	2300	4.6	29.2	0.6	136
29	Vegetable	2010	0	...	...	137
May						
4	20 gms. starch	1700	0	31.3	0.6	139
15	30 gms. starch	2225	trace			
21	30 gms. starch	1875	0	...	...	141
June						
1	40 gms. starch	1780	0	...	...	143
26	60 gms. starch	1500	0	...	...	147
September						
29	60 gms. starch	1870	0	...	...	152

Two strict vegetable days were followed by days of carbohydrate-free diet in rotation until April 18, after which but two vegetable days were given each week. After May 4 the vegetable days were discontinued, but starchy food was used only on alternate days, and on one day each week protein food was confined to eggs and fish. This patient gave complete and intelligent coöperation. He is apparently in perfect health at present, although confined strictly to his diet.

The second example is that of a man twenty-three years of age, who appeared to me to be beyond help when I first saw him. The patient had been confined to bed for three days because of weakness and drowsiness. He could be roused to answer questions but dozed off while attempting to converse. The urine

analysis showed 4.13 grammes of ammonia nitrogen and 219 grammes of sugar. The prognosis seemed almost hopeless.

Infusions of alkalies were given and wine as a beverage. No food was offered the patient for the first thirty-six hours, then he was given oatmeal gruel. The chart shows the details of the treatment.

Date. October	Diet.	Amount urine. c.c.	Sugar. gm.	NH_3–N gm.	Diacetic. gm.
13	Oatmeal	1260	56.7	2.43	+++
15	Oatmeal	640	16.6	1.85	+++
16	Vegetable, strict.	910	11.8	...	+++
17	Vegetable, strict.	890	7.6	0.95	+++
19	Oatmeal	860	1.2	...	+
21	Vegetable, strict.	780	0	...	+
22	20 gms. starch	560	0	...	+
23	20 gms. starch	1380	0	0.55	trace
26	Vegetable	1580	0		
November					
12	60 gms. starch	1460	5.8		
13	C.F.	1280	0		
15	20 gms. starch	1320	0		

In attempting these very rigid courses of treatment there are certain indispensable conditions: the patient must be either in a hospital or under the absolute control of a nurse who understands diabetic diets. The coöperation of the family can be expected in sympathy but not to the extent of denying the patient food. After the critical period is passed the immediate coöperation of the patient is absolutely necessary. It requires no little fortitude in a patient to submit to this routine. The substitution of some bulky food for the fast days advocated by Naunyn does not very

materially assuage the pangs of hunger. The mode of operation of this regimen is not very clear except that there is given an opportunity for a fall in blood sugar. Naunyn advocated fast days to meet this end and used several in succession with severe cases.[6] The ration of green vegetables is a somewhat less heroic measure to this same end. Alcohol is a most valuable therapeutic agent in acidosis, as Neubauer demonstrated, and should be used liberally.

In the treatment of these severe cases of diabetes where acidosis is the chief consideration it is not sufficient to advise a suitable diet. The patients react to the slightest fatigue by an increase in the ketonuria, hence, it becomes necessary to insist on absolute rest in bed. The amounts of alkalies given depend on the ability of the patient to take them. Twenty-five grammes of bicarbonate of soda a day is easily given, with more than this it facilitates administration with some cases to prescribe the soda in enteric capsules.

By the enforcement of rest in bed and a stringent diet the urine can be freed of sugar in the vast majority of cases. With early cases the result is often effected within a few days; when the disease is ad-

[6] In an endeavor to test the Lusk ratio with severe cases of diabetes several years ago, I observed a fall in ketone excretion after the use of very meagre, rigid diets, even when alkalies were given liberally. This appeared as a basis for therapeutic restrictions and has since been employed, although it is against ideas commonly taught. I believe there is no danger, especially when alcohol is used as a safeguard.

vanced and there is a complicating severe acidosis months may be necessary—and for the treatment of these most severe types of the disease no method is of more benefit than the employment of vegetable days and fast days as advocated by Naunyn. These are the most discouraging cases, as they never approach a semblance of health. While it is possible to free the urine of sugar and to build up some tolerance so long as the patient is in bed and in hospital, at once on being released from incessant control there is an inevitable transgression beyond the path of safety in diet and exercise. Life under the necessary conditions is not worth living for all but the very few.

With severe cases of diabetes coma develops finally in spite of the best endeavors. The only means we have at present for treating this condition is with alkalies. Large amounts of sodium bicarbonate or carbonate must be introduced into the body in order to produce any effect. Where coma is already developed an infusion into a vein is necessary and this may be supplemented by enemata. For intravenous infusions one uses sodium carbonate in four per cent. solution. The sodium salt is added to sterile water, as boiling changes the carbonate into the bicarbonate. Of this solution 250 c.c. may be given every four hours. The technic of administration is simple and essentially the same as that employed in giving salvarsan, the only apparatus necessary being a needle of about 20

gauge. In stress of circumstance a douche bag may be used as the reservoir. The solution should be given slowly with not more than three feet of elevation of the reservoir. When coma is not pronounced this measure is occasionally successful. The best way of giving enemata is by the Murphy drip with which four per cent. bicarbonate of soda in physiological salt solution can be given continuously. This procedure has the added advantage of introducing considerable fluid into the body.

Lüthje believes that sugar is better utilized by diabetics when given by rectum and advises the employment of enemata of glucose solutions in severe acid intoxication.

SURGICAL COMPLICATIONS

The complications of diabetes which require surgical treatment can best be considered under two divisions: first, those disorders where the primary disease is an impeding factor to the healing process; and under this head the infections take first rank: second, those disorders wherewith any surgical operation becomes hazardous on account of the danger of coma diabeticum.

Every diabetic is prone to infections such as boils, carbuncles, and various phlegmons; and with the older patients perforating ulcers. The so-called diabetic gangrene and osteomyelitis are very common. All of

these conditions often require some surgical treatment in the beginning; pus collections must be opened and drained. After this initial measure it is a matter of common observation that healing of the wound is excessively sluggish at best and often the area involved extends. This state of affairs is best exemplified with boils and carbuncles which in diabetes may assume menacing severity. One bad boil after another appears and is opened, the patient between physical discomfort and the infection loses weight and strength, becoming constantly less able to withstand new invasions. Death may occur from septicæmia. The failure of these wounds to heal is due fundamentally to the fact that the blood and tissue juices contain an abnormally large amount of glucose. This glucose not only hampers the ordinary reparative reactions in the tissues but it also furnishes a better culture medium for infecting organisms than normal. The proof of this contention is found in the rapid, and at times, astonishing improvement that follows the successful dietetic treatment of the diabetes. The cases that are most apt to present these surgical complications are adults over forty years of age where the diabetes is of a relatively mild type which responds to appropriate treatment. Acidosis is but seldom a menacing factor. The following case is an example. The patient was a man fifty-two years of age who had

had diabetes some six years. He had been advised to abstain from sweets and to use gluten bread. For the last year he had had considerable inconvenience from boils on various parts of the body. For about two months he had a large carbuncle on the back which was opened and still drained freely; shortly after this operation a painful swelling appeared in the left side of the abdomen and was incised; since this last operation there have been some half dozen boils on the arms and shoulders. The patient had lost about thirty pounds in weight during six months. There was a wound with sluggish granulations and much discharge in the left infraspinatus region and in the left rectus muscle just above the umbilicus an ulcer two by three inches, surrounded by a wide area of induration. The ulcer surface was dark in color and discharging freely; granulations were almost absent. The urine contained 48 grammes of sugar. It required six days to free the urine of glucose and on the tenth day the surgeon reported that the ulcers were clean and granulation tissue forming. After this recovery was rapid.

Of far more significance are those infections which result in the condition commonly called diabetic gangrene. Usually the course of events is that the patient first notices on a toe or the ball of the foot a little blister. This is " pricked " or breaks and an ulcer forms, at first small and superficial but gradually

larger and deeper until a wide eroded area exists, involving fascia and tendons. The surrounding tissue is involved in the inflammatory reaction and becomes discolored and finally livid. In some cases no pulsation can be felt in the dorsalis pedis artery. Surgical experience has demonstrated that amputation is a desperate measure. Many cases do not survive the first operation or when they do it is so often found that a failure of healing in the stump necessitates a second operation higher up the leg. One surgeon has summarized his experience with this condition in the dictum that "amputation of the foot should be done at the hip." Surgeons in general admit that operative treatment in these cases is most unsatisfactory and that the mortality is very high. On this account it is at least rational to give some other method a preliminary trial before accepting the radical and desperate course. Surgical measures should be confined to that which is absolutely necessary and can be done without an anæsthetic, such as removing dead tissue from the ulcerated area. The treatment consists in two measures; an appropriate regimen and a dressing to the foot, which should be kept elevated. For the first week a wet dressing[7] of some stimulating solution is best. The foot must be kept at rest elevated on a chair. With bad cases the patient must

[7] Red wash has been found most satisfactory.

be in bed. These cases are easily treated, as the diabetes is usually of the less severe types. The results are, with this method, hardly less than brilliant. A series of cases was published by Adrian V. S. Lambert[8] and some of these patients are known to be in excellent health at present. Gangrene in diabetes, while it has many points of similarity with that observed in senile individuals, is not, however, very often identical. There may be, often is, an extreme arteriosclerosis but apparently there are other factors, perhaps angiospasm; but the difference rests conspicuously in the primary infection with the diabetic. That true gangrene resulting from an endarteritis obliterans may occur in diabetic individuals is not denied, though this is exceptional, the important fact being that the types of gangrene of the extremities usually seen in association with diabetes are amenable to treatment without amputation of the diseased part.

Persons afflicted with diabetes are subject to the same surgical diseases as the rest of mankind. The difference here lies solely in the increased risk of anæsthetics and of the operative procedures. It is sometimes a matter of grave doubt whether the patient can survive on account of a complicating acidosis. The question arises then as to how to determine whether an operation can be undertaken at all,

[8] Annals of Surgery, 1914.

or with what degree of increase in the risk. With a young diabetic individual who manifests a considerable degree of acid intoxication it may be stated with confidence that an anæsthetic would precipitate coma. Whether an operation can be considered in any case depends primarily on the degree of acidosis and this may best be indicated by the ammonia of the urine. If the ammonia is over two grammes per day a severe operation would be hazardous in the extreme; if three grammes per day, out of the question. It is possible with some cases by suitable treatment to reduce the acidosis to an amount permitting an urgent surgical procedure. But in cases of this type it must be constantly borne in mind that the patient is not normal and the post-operative treatment should be directed to meet a developing acidosis. With what has already been said relative to infections further statement is hardly demanded to point out the advantage of suitable dietetic treatment during the convalescent period. The repair of the wound is hastened and the possibility of infection diminished.

FRESH VEGETABLES THAT CONTAIN OVER FIVE PER CENT. OF CARBOHYDRATES.

	Per cent.	Gm. equivalent to 10 gm. o f bread
Radishes	5.0	..
Leeks	6.0	..
Mushrooms	6.0	..
String beans	6.0	..
Turnips	6.0	90
Kohl-rabi	7.0	76
Oyster plant	7.0	76
Rutabaga	7.0	76
Squash	8.0	66
Beets	9.0	59
Carrots	9.0	59
Onions	9.0	56
Parsnips	11.0	48
Peas	15.0	35
Lima beans	22.0	24
Potatoes	20.0	27
Corn	19.0	27

CANNED VEGETABLES THAT CONTAIN OVER FIVE PER CENT. OF CARBOHYDRATES.

	Per cent.	Gm. equivalent to 10 gm. of bread
Corn	18.0	29
Succotash	18.0	29
Beans, haricots verts	2.0	..
Tomatoes	3.0	..
Peas	10.0	53
Squash	10.0	53
Beans, haricots flageolets	11.0	48
Beans, lima	13.0	41
Beans, baked	17.0	31
Beans, red kidney	17.0	31

FRESH FRUITS THAT CONTAIN OVER FIVE PER CENT. OF CARBOHYDRATES.

	Per cent.	Gm. equivalent to 10 gm. of bread.
Strawberries	5.0	106
Grape-fruit	6.0	88
Watermelon	7.0	76
Blackberries	8.0	66
Cranberries	8.0	66
Peaches	9.0	59
Muskmelon	10.0	53
Raspberries	10.0	53
Apples	11.0	48
Pears	11.0	48
Apricots	12.0	44
Gooseberries	12.0	44
Pineapple	12.0	44
Currants	13.0	41
Oranges	13.0	41
Huckleberries	17.0	31
Bananas	20.0	27

NUTS THAT CONTAIN OVER FIVE PER CENT. OF CARBOHYDRATES.

	Per cent.	Gm. equivalent to 10 gm. of bread.
Butternuts	3.5	..
Brazil-nuts	9.0	88
Hickory-nuts	11.0	48
Pecans	11.0	48
Filberts	12.0	44
Beechnuts	13.0	41
Walnuts, English	13.0	41
Almonds	16.0	33

MISCELLANEOUS

Plain chocolate	25.0
Cocoa	38.0
Cocoa nibs, roasted	28.0

FOODS SUITABLE FOR DIABETIC PATIENTS.[9]

Under Five Per Cent. Carbohydrate.

Milk, sugar-free (Whiting and Sons, Rutherford Ave., Boston)	.0
Marmalade, casoid sugarless	1.2
Jam, casoid sugarless	2.1
Dinner rolls, casoid sugarless	2.2
Casoid flour (Thomas Leeming and Co., 99 Chambers St., New York)	2.2
Gluten biscuits 80 per cent. (Kellogg Food Co., Battle Creek, Michigan)	4.4

From Five to Ten Per Cent. Carbohydrate.

Casoid biscuits, No. 2	5.6
Rademanns preserved fruits "in eigenem Saft" (Muller and Co., 11 West 27th St., New York)	5.7
Akoll biscuits, Huntley and Palmer (Hazard and Co., 29 Broadway, New York)	6.5
Rademanns preserved fruit "ohne Zucker"	7.0

Over Ten Per Cent. Carbohydrate.

Proto puffs, No. 1 (Health Food Co., 25 Lexington Ave., New York)	11.9
Plasmon cocoa (Plasmon Co., London, England)	20.9
Soy bean flour (Cereo Co., Tappan, N. Y.)	23.7

[9] Analyses from Report Conn. Agriculture Experiment Station. Report 1913, Part I, Section 1, Diabetic Foods.

The diabetic patient feels the restriction in his diet mostly in the absence of bread. The great majority of gluten breads and flours are shameful frauds —and are absolutely useless. There are a few preparations available which are permissible, and a list of these is appended. A palatable muffin can be made from soybean flour for which the New York Hospital Diet Kitchen has this recipe:

Soybean Muffins

1 cup soybean flour
2 tablespoonfuls wheat flour
½ tablespoonful salt
2 teaspoonfuls baking powder
Sift all together and add—
¾ cup milk
1 egg beaten
2 tablespoonfuls melted butter
Pour into muffin tins and bake twenty minutes.

These muffins each contain 10 grammes of carbohydrate.

Casoid flour may be used advantageously as follows:

Casoid Bread

3 eggs
Pinch of salt
½ cup Casoid flour

Separate whites and yolks; add salt to yolks; beat separately, and add yolks to whites. Then fold in, with as little stirring as possible, the flour. Bake in a greased pan with a hollow centre, such as is used for sponge cake, in an oven not too hot at first but with increasing heat, for twenty minutes or half an hour. If not allowed to cool too quickly it will retain its lightness better.

Recipe by Mrs. Douglass C. Moriarta.

XIV

IDENTIFICATION OF SUGARS

While it is not probable that any mistake ever occurs in identifying glucose in the urine of a patient with definite symptoms of diabetes the misinterpretation of slight reduction tests is, however, common. It is known, too, that more than one carbohydrate may be present in some diabetic urines. The following tests are of service in recognizing and identifying small amounts of sugar. These procedures cannot well be undertaken except in hospital laboratories and they also require some familiarity with chemical manipulations.

Various sugars other than glucose may occur in urine, and some substances not sugar can simulate the reducing reactions of sugar. Albumen or other proteins must before the tests be removed from the urine. For routine examinations of urine the tests usually employed are dependent upon reduction of a metallic salt. In this country Fehling's solution is generally given preference. When carefully manipulated Fehling's solution is a delicate reagent capable of detecting 0.1 per cent. of glucose. It reacts to all reducing sugars and also to some of the normal in-

gredients of urine such as uric acid and creatinine, when these are present in some degree of concentration. Several methods of employing Fehling's solution have been advised in order to minimize the sources of error. The solution should not be boiled after the urine is added; it is perhaps the best way to allow the test tube to stand in a boiling water bath. Many of the difficulties inherent in the use of Fehling's solution for routine examinations are avoided by employing Benedict's reagent. Not only is this reagent not sensitive to normal urinary ingredients but it is also more delicate than Fehling's in its response, reducing sugars reacting to as low as 0.01 per cent. of glucose. In performing a test one uses about 5 c.c. of reagent and 5 to 10 drops of urine. The mixture is boiled vigorously for two minutes and then allowed to cool. When a reduction takes place there separates out a precipitate which may be red, yellow or greenish in color. A slight turbidity which may form without precipitation is due to urates and offers no source of confusion. This reagent does not react to uric acid nor creatinine; it is, however, affected by glucuronic acid.

Some urinary substances that reduce copper salts do not reduce bismuth salts. This is true of glucuronic and homogentisic acids, and accordingly Nylander's solution is a valuable aid in differentiating these substances from sugar. The use of Nylander's solution

in doubtful cases is a valuable supplement to the alkaline copper solutions. Protein must be removed from urine before conducting tests with Nylander's solution.

That a urine gives a reduction test is not sufficient evidence of the presence of sugar even when the reaction is undoubted. It becomes necessary to utilize other tests for confirmation and among these fermentation and polarization are of chief value.

In practice it is customary to "run controls" on all fermentation tests—as follows: a piece of brewer's yeast the size of a pea is emulsified with 5 c.c. of water. Two drops of this are added (1) to the urine to be tested, (2) to normal urine, (3) to normal urine which has had a little glucose dissolved in it. The controls answer the questions: does the yeast alone evolve gas, and is it capable of fermenting glucose? When the sample under examination evolves gas the contents of the fermentation tube should be filtered and tested again for reduction (and rotation).

Monosaccharides	Reduction.	Barfoed reaction.	Ferment.	Rotation.
Pentoses	+	0	0	0
Hexoses, Glucose	+	+	+	*d*
Levulose	+	+	+	*l*
Galactose	+	+	0	*d*
Disaccharides				
Maltose	+	0	+	*d*
Lactose	+	0	0	*d*
Glucuronates	+	0	0	*l*
Glucuronic acid	+	0	0	*d*

Sugars may be divided into those that are quickly fermented at a temperature of 38° C. (100° F.) within 18 hours (glucose, levulose, maltose) and those that require 24 to 36 hours for decomposition (lactose, galactose, isomaltose). This difference may sometimes be utilized as a clue in tests for identification.

There is no gas formation with pentose nor with the glucuronic acid compounds and reduction of alkaline copper solutions will occur both before and after fermentation. Lactose and galactose are not fermentable by yeast but bacteria present in commercial yeast may effect decomposition.

The rotating powers of the various sugars serve as important evidence towards their identification. The following classification is based on the polarimetric action of these substances. Dextrorotatory: glucose, galactose, lactose, maltose. Lævorotatory: levulose and most glucuronates (oxybutyric acid and proteins). Inactive: pentose.

Polarimetric readings taken both before and after fermentation frequently offer results that confirm other tests. If only glucose or levulose be present the rotation after fermentation is the rotation of normal urine (1., .05°–.10°). When besides glucose, β-oxybutyric acid or glucuronic acid compounds are present in the urine the fermented specimen is lævorotatory.

Maltose deflects polarized light more than does glucose while its reducing power on alkaline copper solutions is much less. Hence when a urine containing maltose is examined a wide discrepancy between the readings and titrations is noted and after such a urine is boiled with acid the polariscope readings decrease but the reduction of Fehling's increases. The prosecution of these tests as outlined will give evidence sufficient to identify the sugars commonly found in urine; for complete proof confirmatory reactions are demanded. A urine which causes reduction and is dextrorotatory before fermentation but is inactive afterwards probably contains glucose.

Before applying the more delicate tests for the identification of sugars it saves time and increases the definiteness of these tests to remove from the urine as much of the nitrogenous organic matter as possible. This may be done in several ways: (1) basic lead acetate will precipitate pigments, some salts and glucuronic acid. The excess of lead is removed from the filtrate by precipitating with hydrogen sulphide. (2) Mercuric nitrate precipitates nitrogenous materials quite completely. The excess of mercury is removed from the filtrate as the sulphide with H_2S. (3) Phosphotungstic acid is an excellent "clearing" reagent; the excess being precipitated with barium hydrate

from the filtrate and then after filtering any excess of barium is thrown down by CO_2. Charcoal cannot be employed, as it adsorbs sugar in appreciable amounts. By using one of these preliminary steps a water-clear material is secured which facilitates the tests to be employed.

Barfoed Reaction.—The reagent is a 0.5 per cent. solution of copper acetate in 0.1 per cent. acetic acid. To 5 c.c. of this reagent add 10 drops of urine and heat in a water bath 5 minutes. A yellowish or reddish precipitate indicates the presence of sugar. This reaction is characteristic for monosaccharides: glucose, levulose, and galactose.

Levulose.—Seliwanoff's Reaction: The reagent consists of 0.5 grammes of resorcin, 30 c.c. of concentrated hydrochloric acid and 30 c.c. of water. Equal parts of the urine and this reagent are mixed and heated on the water bath. When levulose is present a magenta color develops promptly. On cooling a red precipitate separates out. The acid may now be neutralized with sodium carbonate and the solution extracted with amyl alcohol to which is imparted a red color. On examining with the spectroscope a band appears between *E* and *B*.

Pentose.—Orcin Test; Bial's Method. Reagent: 100 c.c. concentrated hydrochloric acid (reagent,

specific gravity 1.195) 0.2 gramme orcin, and 5 drops of a 10 per cent. solution of ferric chloride. Heat 5 c.c. of this reagent to boiling, remove from the flame and add the urine drop by drop, using not over 1 c.c. The characteristic reaction is a greenish color which appears quite promptly. On cooling, the mixture is extracted with amyl alcohol, which takes up a blue-green color. An absorption band between *C* and *D* is found on spectroscopic examination. Glucuronic acid gives the same result.

Phloroglucin Test: See under Lactose.

Lactose.—Malfetti-Wöhlk Test: Mix 5 c.c. of urine; 3-5 c.c. of strong ammonia and 5 drops of potassium hydroxide (10 per cent.). The mixture is warmed in the water bath. A red coloration develops in three or four minutes. This reaction is also given by maltose. With glucose the color is brown or yellowish.

Mucic Acid Test: To 150 c.c. of urine add 20 c.c. concentrated nitric acid (specific gravity 1.4) and allow to stand on a boiling water bath until the material is a clear yellow color. Allow to stand 24 hours in a cool place. Any precipitate that has formed during this time is filtered off, washed with cold water and dissolved in a small amount of boiling water from which the crystals reform on cooling. Mucic acid has a melting point of 215° to 225°, depending on its

purity. On dry distillation mucic acid yields pyrrol, which is recognized by the red color imparted to a pine splinter that has been moistened with hydrochloric acid. The mucic acid is formed from galactose resulting from the hydrolysis of lactose, hence the former also yields the test as well as the latter.

Phloroglucin Test (Salkowski): To 10 c.c. of concentrated hydrochloric add enough phloroglucin so that some remains undissolved after warming the mixture. Decant the acid into a test tube, add 10 drops of urine and place the test tube in a water bath. A positive reaction is indicated by a red color beginning above and extending downward. The heating must not be continued after the color has appeared. After cooling the pigment may be extracted with amyl alcohol and examined spectroscopically. Pentose and glucuronic acid yield absorption bands between *D* and *E;* lactose and galactose none. The color is yielded by lactose, galactose, pentose and glucuronic acid.

The identification of a sugar cannot be completely established without the aid of the hydrazine compounds. With phenylhydrazine and with substitution products of it the sugars form hydrazones and osazones which, in their solubilities, melting points, and optical activities, are characteristic.

In preparing glucosazone the urine may be used

without previous treatment when the amount of sugar is large; if but only small amounts of a reducing substance be present it is advisable first to remove salts and nitrogenous matter as already indicated and concentrate the material before conducting the tests.

Glucosazone may be prepared as follows: Mix 5 grammes of phenylhydrazine hydrochloride, 10 grammes of sodium acetate, and 10–15 c.c. of urine in a test tube and warm; if the salts do not all dissolve add more water. Allow the mixture to stand in hot water for half an hour and then cool. A yellow crystalline precipitate of glucosazone separates out. The crystals are filtered off and recrystallized from hot alcohol.

Besides the compounds formed by the several sugars with phenalhydrazine, there are various hydrazones and osazones derived from diphenyl and methylphenylhydrazine. These all differ to a degree in their solubilities in water, alcohol, etc., which fact is utilized in separating mixtures of sugars. For example dextrose forms with diphenylhydrazine a hydrazone which is insoluble in water; while that of levulose is soluble. All of the hydrazine compounds are soluble in pyridine-alcohol and this is the solvent used in determining the specific rotation: 0.2 gramme of the osazone, 4 grammes of pyridine and 6 grammes of absolute ethyl alcohol.

The accompanying chart contains the data ordinarily required.

OSAZONES AND HYDRAZONES

	Phenylhydrazine.				Melting points.	
	Solubility.		Specific rotation.	Melt at	Methyl-phenyl-hydrazine.	Diphenyl-hydrazine.
	Water.	CH_3OH				
Glucose	I	sl	−1.3°	205°	130°	162°
Levulose	I	sl	−1.3°	205°	160°	
Galactose	sl	s	+ .48°	195°	180°	157°
Lactose	1:90 100°	s	±0.0	210°		
Maltose	1:70 100°	s	+1.3°	205°		
Iso-maltose	1:4 100°	s	.....	150°		
Pentose	?s 60°	s	+1.1°	165°	164–173°	205–216°
Glucuronic acid	sl	s	left	115°		

s, soluble; I, insoluble; sl, slightly soluble.

NYLANDER'S TEST.—The reagent is prepared by dissolving 2 grammes of bismuth subnitrate and 4 grammes of Rochelle salt in 100 c.c. of 10 per cent. potassium hydroxide solution. The reagent is filtered.

To 5 c.c. of urine in a test tube add one-tenth its volume of Nylander's reagent and heat for five minutes in a boiling water bath. Reduction is indicated by a darkening in the color of the mixture due to the precipitation of bismuth.

Hæmatoporphyrin, indican, urochrome, and uroerythrin may be sources of confusion.

FEHLING'S SOLUTION.—Cupric Sulphate Solution: Dissolve 34.65 grammes of cupric sulphate in water and make up to 500 c.c.

Tartrate Solution: Dissolve 125 grammes of potassium hydroxide and 173 grammes of Rochelle salt in water and dilute to 500 c.c.

These solutions should be filtered and kept in rubber-stoppered bottles. Equal volumes are mixed when needed for tests.

BENEDICT'S REAGENT.—Qualitative:

Copper sulphate (pure crystallized)	17.3 gm.
Sodium or potassium citrate	173.0 gm.
Sodium carbonate (crystallized)	200.0 gm.
Distilled water to make	1000.0 c.c.

Dissolve the citrate and carbonate together with the aid of heat in 700 c.c. of water. Filter if necessary. Dissolve the copper sulphate in 100 c.c. of water and then pour slowly into the first solution with constant stirring. After cooling, the mixture is diluted to one litre. This reagent may be kept indefinitely without deterioration, and is not appreciably reduced by creatinine, uric acid, the simple aldehydes, homogentisic acid, or glucuronic acid.

BENEDICT'S REAGENT.—Quantitative:

Copper sulphate (pure crystallized)	18.0 gm.
Sodium carbonate (crystallized)	200.0 gm.
Sodium or potassium citrate	200.0 gm.
Potassium sulphocyanate	125.0 gm.
Five per cent. potassium ferrocyanide solution	5.0 c.c.
Distilled water to make	1000.0 c.c.

With the aid of heat dissolve the carbonate, citrate, and sulphocyanate in enough water to make about 800.0 c.c. of the mixture, and filter if necessary. Dissolve the copper sulphate in 100 c.c. of water and pour the solution slowly into the other liquid, with constant stirring. Add the ferrocyanide, cool, and dilute to exactly 1 litre (measuring flask). Of the various ingredients the copper salt only need be weighed with exactness. 25 c.c. of this reagent are reduced by 50 mg. of glucose.

The urine, 10 c.c. of which should be diluted with water to 100 c.c. (unless the sugar content is believed to be low), is poured into a 50 c.c. burette up to the zero mark; 25 c.c. of the reagent are measured with a pipette into a porcelain evaporation dish (25 to 30 cm. in diameter), 10 to 20 grammes of crystallized sodium carbonate (or one-half the weight of the anhydrous salt) are added, together with a small quantity of powdered pumice stone or talcum, and the mixture heated to boiling over a free flame until the carbonate has entirely dissolved. The diluted urine is now run in from the burette, rather rapidly, until a chalk-white precipitate forms and the blue color of the mixture begins to lessen perceptibly, after which the solution from the burette must be run in, a few drops at a time, until the disappearance of the last trace of blue color, which marks the end-point. The

solution must be kept vigorously boiling throughout the entire titration. If the mixture becomes too concentrated during the process, water may be added from time to time to replace the volume lost by evaporation. The calculation of the percentage of sugar in the original sample of urine is very simple. The 25 c.c. of copper solution are reduced by exactly 50 mg. of glucose. Therefore the volume run out of the burette to effect the reduction contained 50 mg. of sugar. When the urine is diluted 1 to 10, as in the usual titration of diabetic urines, the formula for calculating the percentage of sugar is the following:

$$\frac{0.050}{x} \times 1000 = \text{per cent. in original sample,}$$

wherein x is the number of cubic centimetres of the diluted urine required to reduce 25 c.c. of the copper solution.

When the amount of sugar is small the volume of urine required for reduction of the copper may impart to the reagent a confusing color, which is controlled nicely by adding two teaspoonfuls of powdered calcium carbonate to the reagent.

DETERMINATION OF GLUCOSE IN BLOOD

Benedict-Lewis Method.—Following is the procedure for glucose estimation: Two c.c. of blood (or less if desired) are aspirated from a vein through a hypodermic needle and a piece of rubber tubing into

an Ostwald pipette, a little powdered potassium oxalate in the tip of the pipette preventing clotting. The blood is drawn up a little above the mark on the pipette and, after disconnecting the rubber tubing, is allowed to flow back to the mark. Exactly 2 c.c. are then discharged at once into a 25 c.c. volumetric flask containing 5 c.c. of cold water. The pipette is rinsed once with water and the flask is shaken well to insure thorough mixing. In this manner the blood is laked, a matter of importance, for the corpuscles contain some sugar that would otherwise be lost. Fifteen c.c. of saturated picric acid solution are then added, the contents of the flask are made up to the mark with water and then shaken. After filtration 8 c.c. aliquots are measured out into large Jena test tubes for duplicate determinations. Two c.c. of saturated picric acid solution and 1 c.c. of 10 per cent. sodium carbonate are added (as well as 2 glass beads and 2 to 3 drops of albolene) and the contents of the flask are evaporated rapidly over a direct flame until precipitation occurs. About 5 c.c. of water are added, the test tube is again heated to boiling to dissolve the precipitate, the contents of the tube are quantitatively transferred to a 10 c.c. volumetric flask, cooled, made up to the mark, shaken, and then filtered through cotton into the colorimeter chamber. The color (set at 10 mm.) is compared with that obtained from 0.64

mg. of dextrose, using 5 c.c. of saturated picric acid and 1 c.c. of 10 per cent. sodium carbonate proceeding in the manner described for the aliquot of the blood filtrate. Instead of running a " standard " for each determination we use a solution of picramic acid which has been standardized against the color obtained from 0.64 mg. of dextrose. This permanent standard will keep indefinitely. The calculation is, of course, very simple. The 8 c.c. aliquots is equivalent to 0.64 c.c. of blood.

About 0.07 gm. of picramic acid is treated with about 25 c.c. H_2O and 0.2 gm. Na_2CO_3 warmed until complete solution is effected; cooled and diluted to one litre. The solution may be standardized at once and will keep indefinitely.

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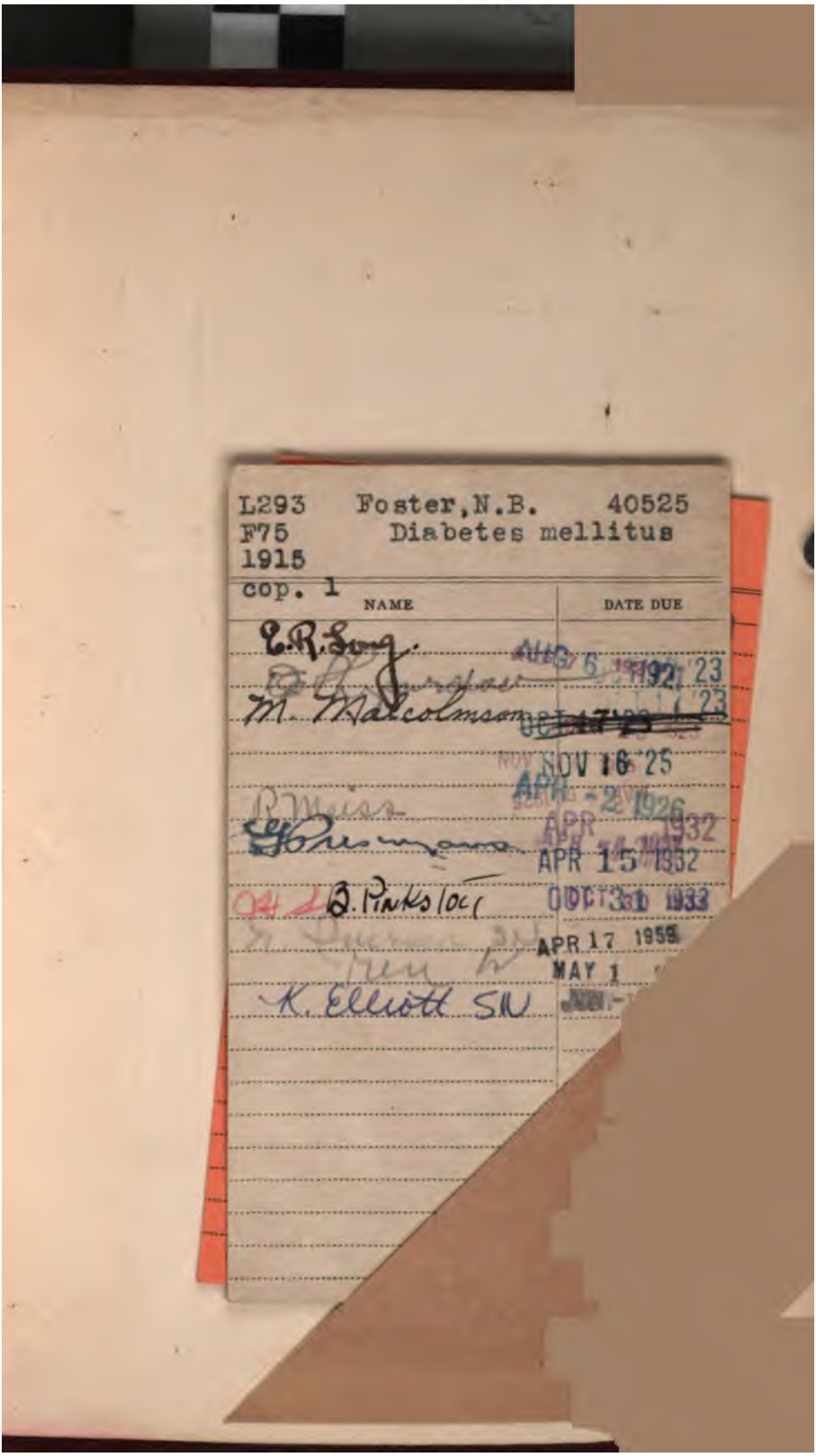

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